UniversitätsKlinikum Heidelberg

SEKTION SEPSIS & SYSTEMISCHE INFLAMMATION
www.sep-sys.de

Therapie der Sepsis

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Erklärung zu Interessenkonflikten

Vortragshonorare:

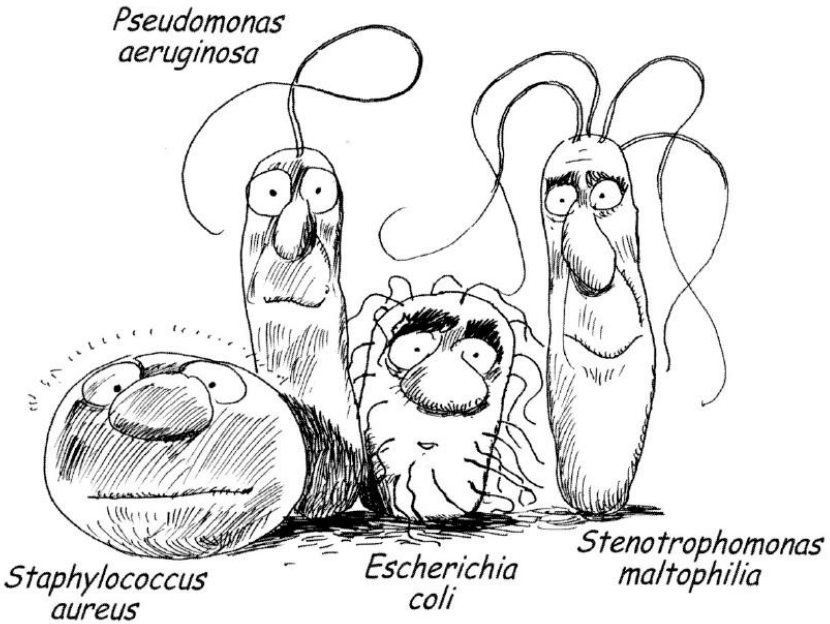
Astellas Pharma,
Astra Zeneca
BBraun
Biosyn
CLS Behring
Eli Lilly
GE-Healthcare
Gilead
Glaxo Smith Kline
Janssen
Köhler Chemie
MSD Sharp & Dohme
Novartis
Orion
Pfizer Pharma

Advisory Boards:

Astellas Pharma,
BBraun
Gilead
MSD Sharp & Dohme
Pall Medical
Pfizer Pharma

Gliederung

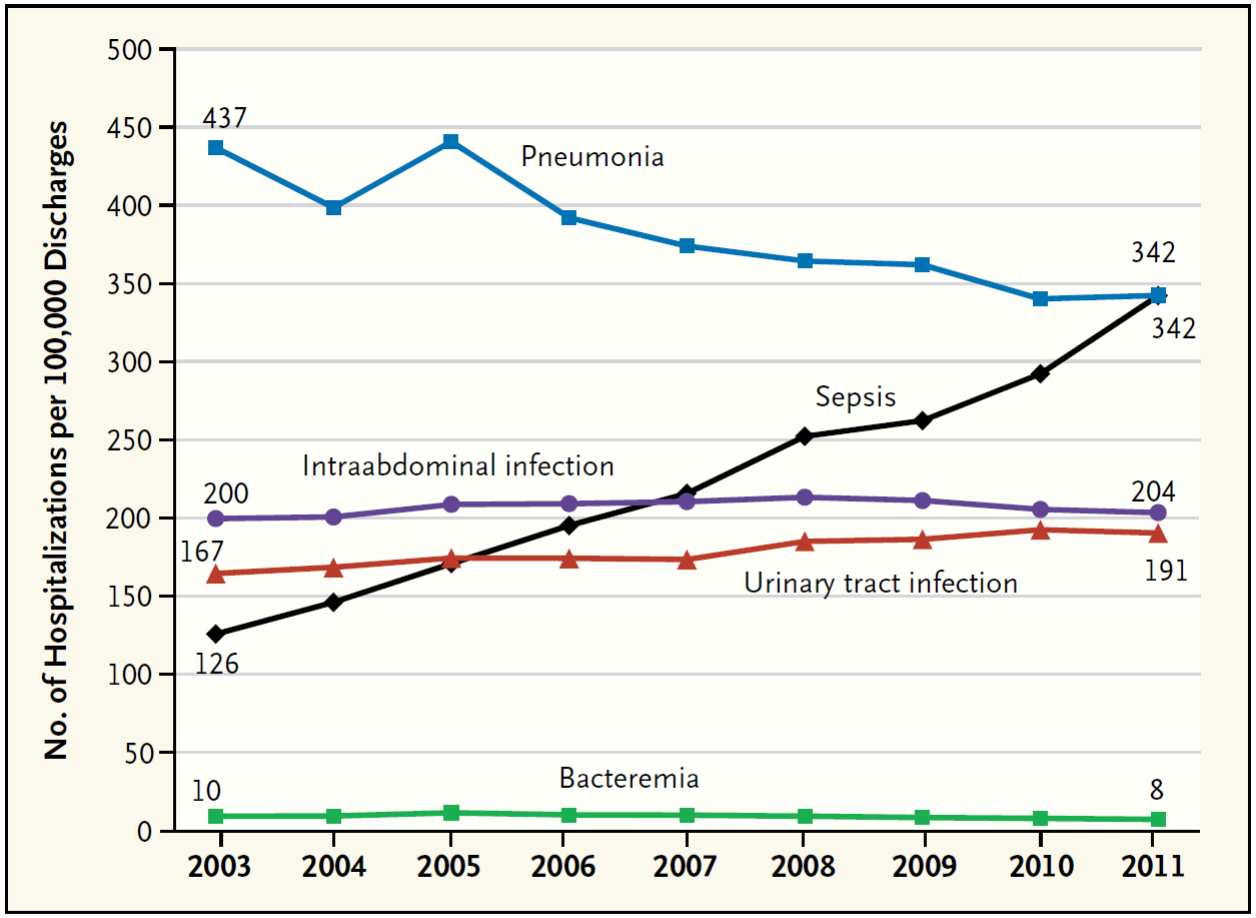
- Einführung und Diagnostik
- Therapie
    - 3h bundle
    - 6h bundle
- Adjunktive Therapie
- Zusammenfassung




FINISH
Alle 3 Sekunden stirbt ein Mensch an Sepsis !
dkfz.
LEKI

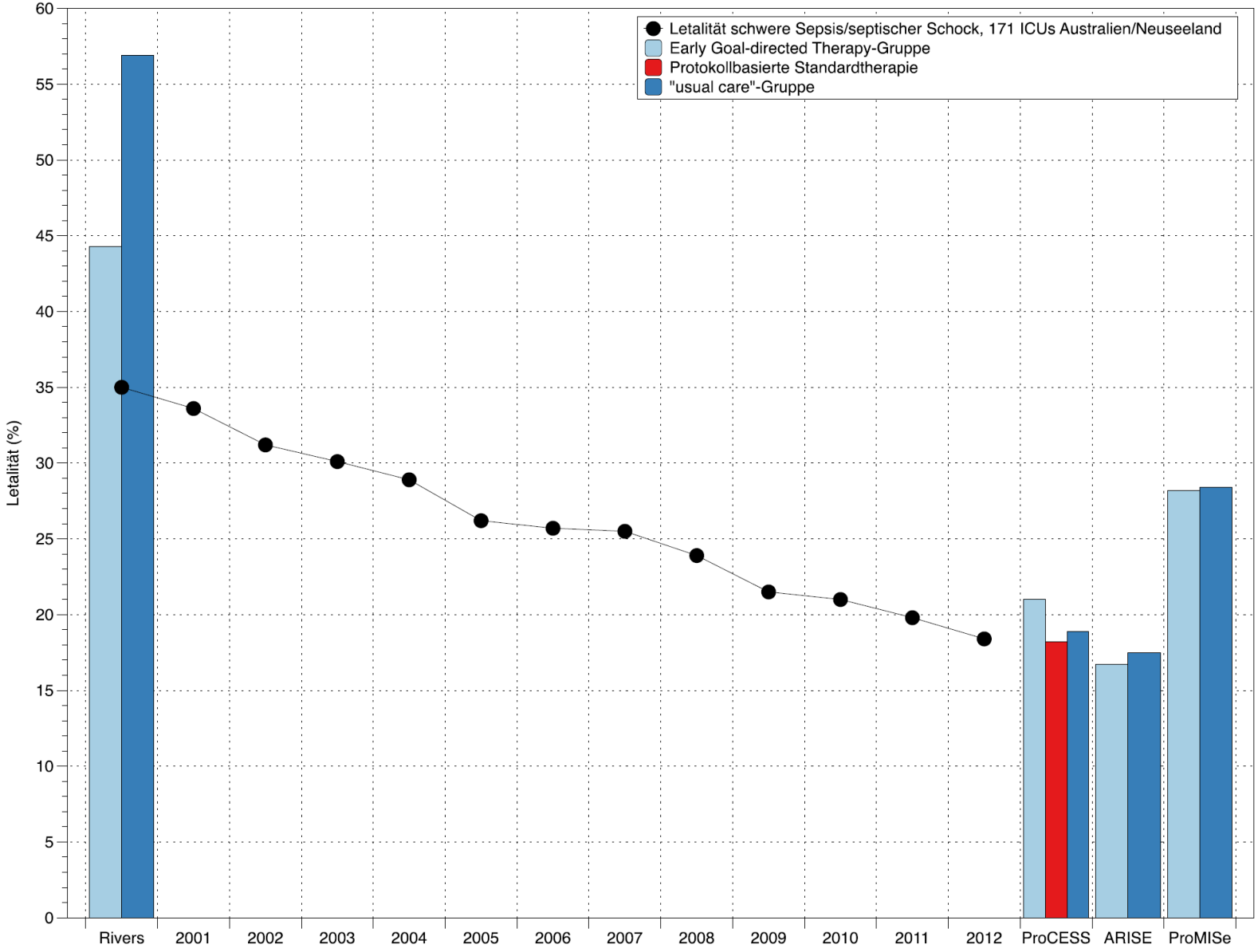
Regulatory Mandates for Sepsis Care — Reasons for Caution

Chanu Rhee, M.D., Shruti Gohil, M.D., M.P.H., and Michael Klompas, M.D., M.P.H.



Hospitalizations for Which Certain Infection Codes Were Listed as a Primary Diagnosis, 2003–2011.

11. Kaukonen KM, Bailey M, Suzuski S, Pilcher D, Bellomo R (2014) Mortality related to severe sepsis and septic shock among critically ill patients in Australia and New Zealand, 2000-2012. JAMA 311: 1308-1316



Die Sterblichkeit der Sepsis ist inadäquat hoch

	Fälle	Todesfälle	Letalität
Sepsis (R65.0)	86.805	8.486	9,8%
Schwere Sepsis (R65.1)	70.054	28.811	41,1%
Septischer Schock (R57.2)	19.233	11.597	60,4%

Tabelle von FM Brunkhorst (2013) basierend auf Daten des Bundesamtes für Statistik

Diagnose und Therapie der Sepsis

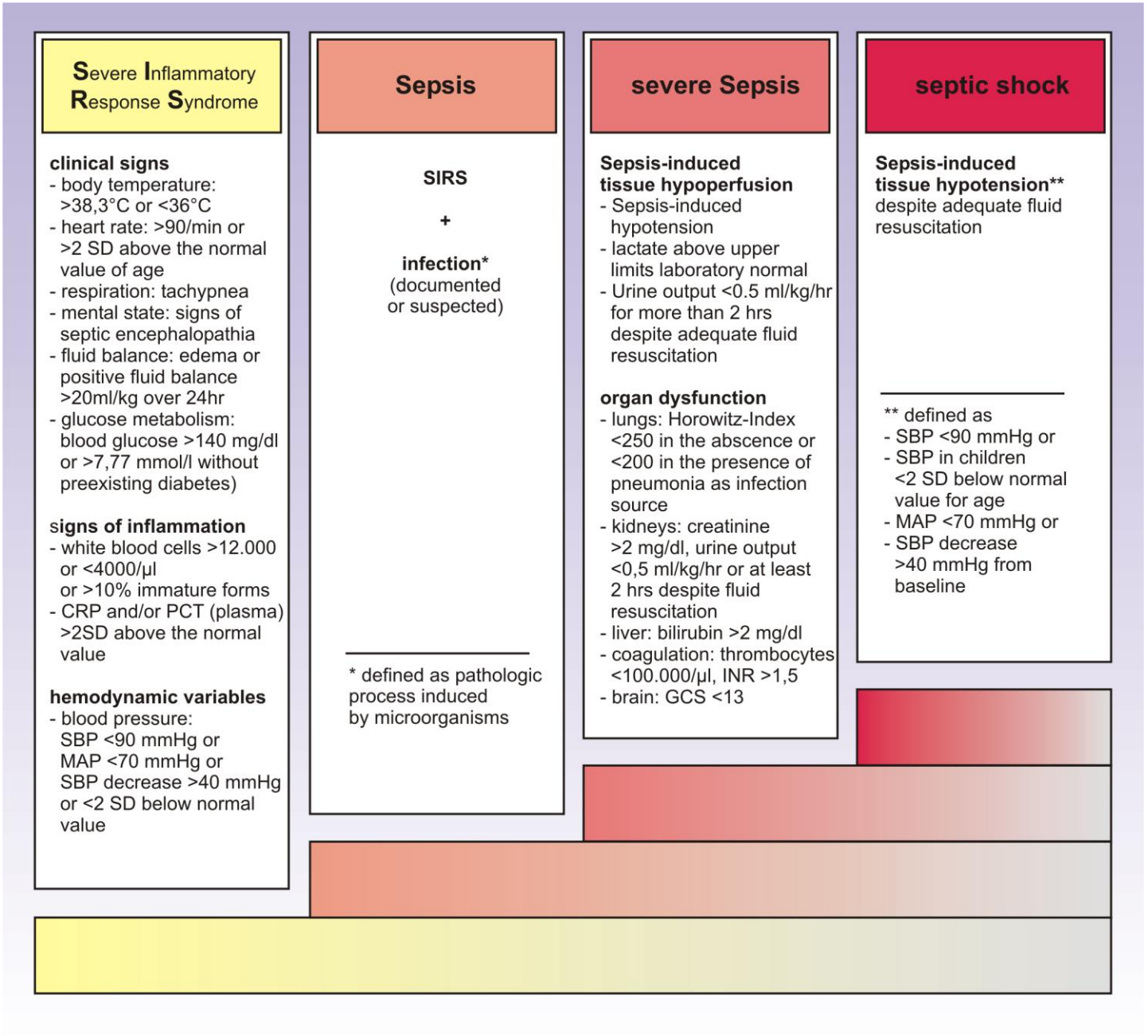
Empfehlungen der Deutschen Sepsis-Gesellschaft e.V.

Diagnose der Infektion — *Blutkulturen*

Klinischer Verdacht auf eine Sepsis bzw. eines oder mehrer der folgenden Kriterien: Fieber, Schüttelfrost, Hypothermie, Leukozytose, Linksverschiebung im Differentialblutbild bzw. eine Neutropenie sind Indikationen für die Abnahme von Blutkulturen.

- Empfehlung Grad C

http://www.uni-duesseldorf.de/awmf/

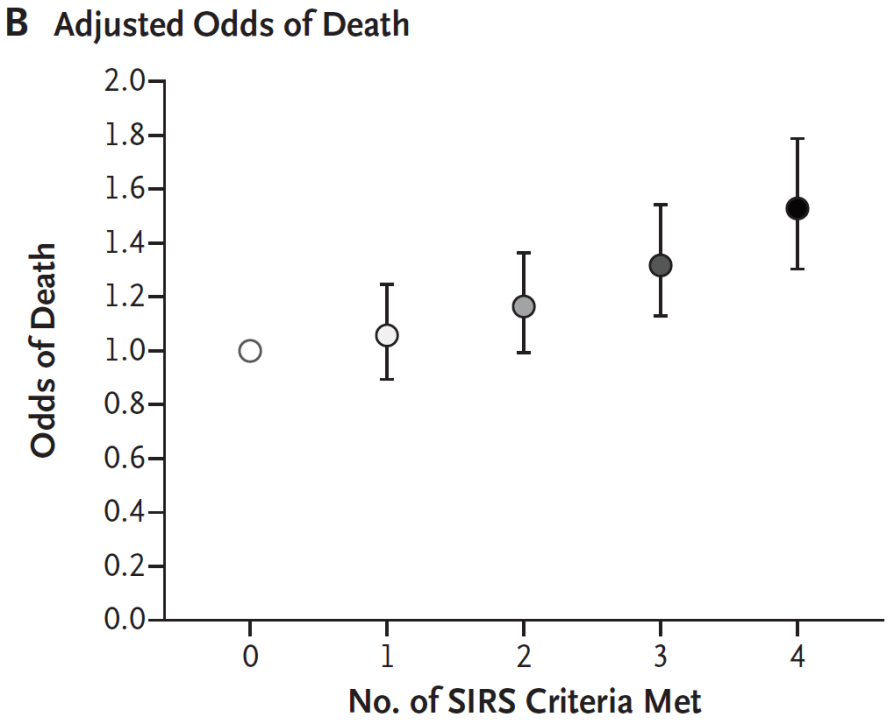

Severe Inflammatory Response Syndrome
clinical signs
- body temperature: >38,3°C or <36°C
- heart rate: >90/min or >2 SD above the normal value of age
- respiration: tachypnea
- mental state: signs of septic encephalopathia
- fluid balance: edema or positive fluid balance >20ml/kg over 24hr
- glucose metabolism: blood glucose >140 mg/dl or >7,77 mmol/l without preexisting diabetes)
signs of inflammation
- white blood cells >12.000 or <4000/µl or >10% immature forms
- CRP and/or PCT (plasma) >2SD above the normal value
hemodynamic variables
- blood pressure: SBP <90 mmHg or MAP <70 mmHg or SBP decrease >40 mmHg or <2 SD below normal value
Sepsis
SIRS
+
infection* (documented or suspected)
* defined as pathologic process induced by microorganisms
severe Sepsis
Sepsis-induced tissue hypoperfusion
- Sepsis-induced hypotension
- lactate above upper limits laboratory normal
- Urine output <0.5 ml/kg/hr for more than 2 hrs despite adequate fluid resuscitation
organ dysfunction
- lungs: Horowitz-Index <250 in the abscence or <200 in the presence of pneumonia as infection source
- kidneys: creatinine >2 mg/dl, urine output <0,5 ml/kg/hr or at least 2 hrs despite fluid resuscitation
- liver: bilirubin >2 mg/dl
- coagulation: thrombocytes <100.000/µl, INR >1,5
- brain: GCS <13
septic shock
Sepsis-induced tissue hypotension** despite adequate fluid resuscitation
** defined as
- SBP <90 mmHg or
- SBP in children <2 SD below normal value for age
- MAP <70 mmHg or
- SBP decrease >40 mmHg from baseline

ORIGINAL ARTICLE

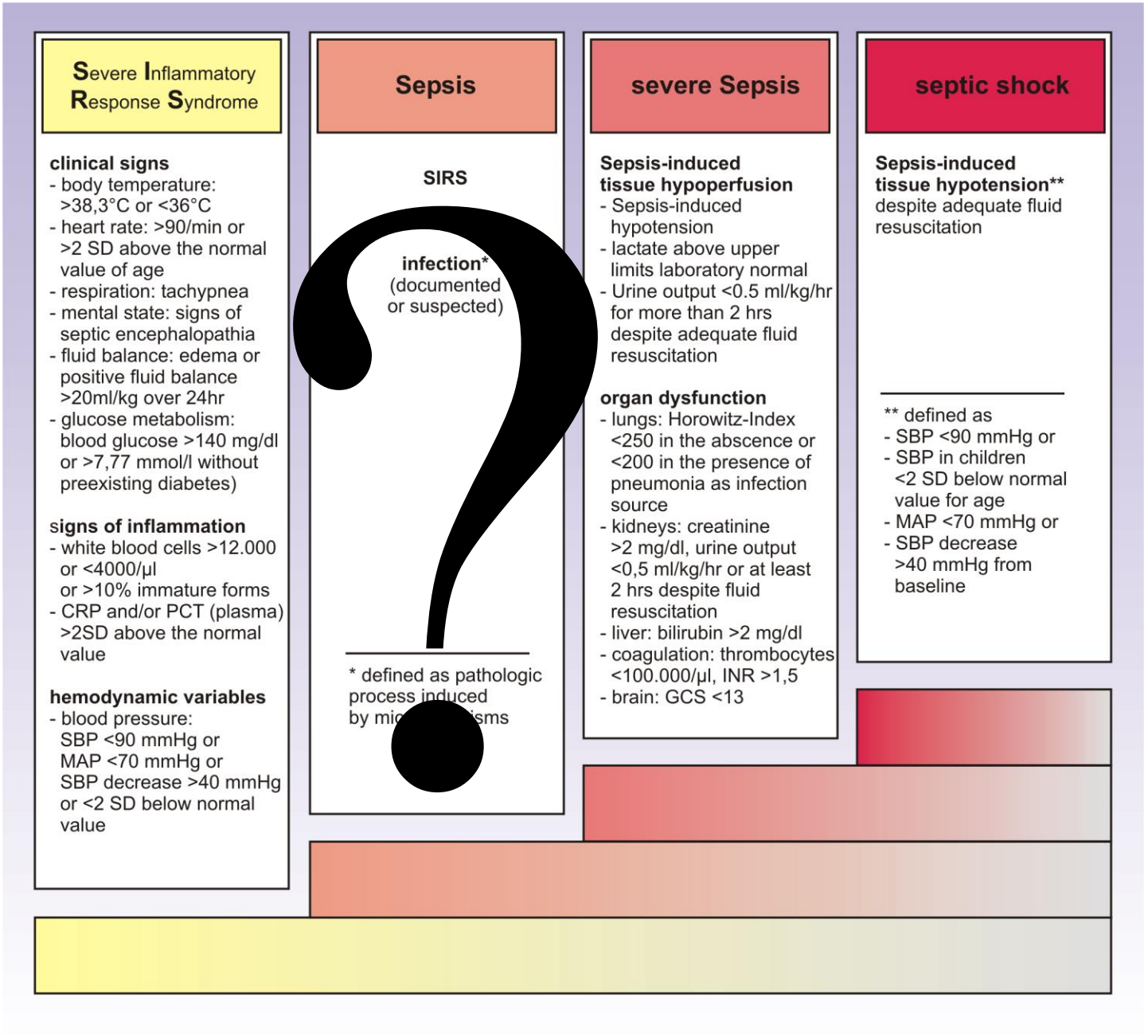
Systemic Inflammatory Response Syndrome Criteria in Defining Severe Sepsis

N Engl J Med 2015;372:1629-38.

Kirsi-Maija Kaukonen, M.D., Ph.D., Michael Bailey, Ph.D., David Pilcher, F.C.I.C.M., D. Jamie Cooper, M.D., Ph.D., and Rinaldo Bellomo, M.D., Ph.D.



The need for two or more SIRS criteria to define severe sepsis excluded one in eight otherwise similar patients with infection, organ failure, and substantial mortality and failed to define a transition point in the risk of death. (Funded by the Austra-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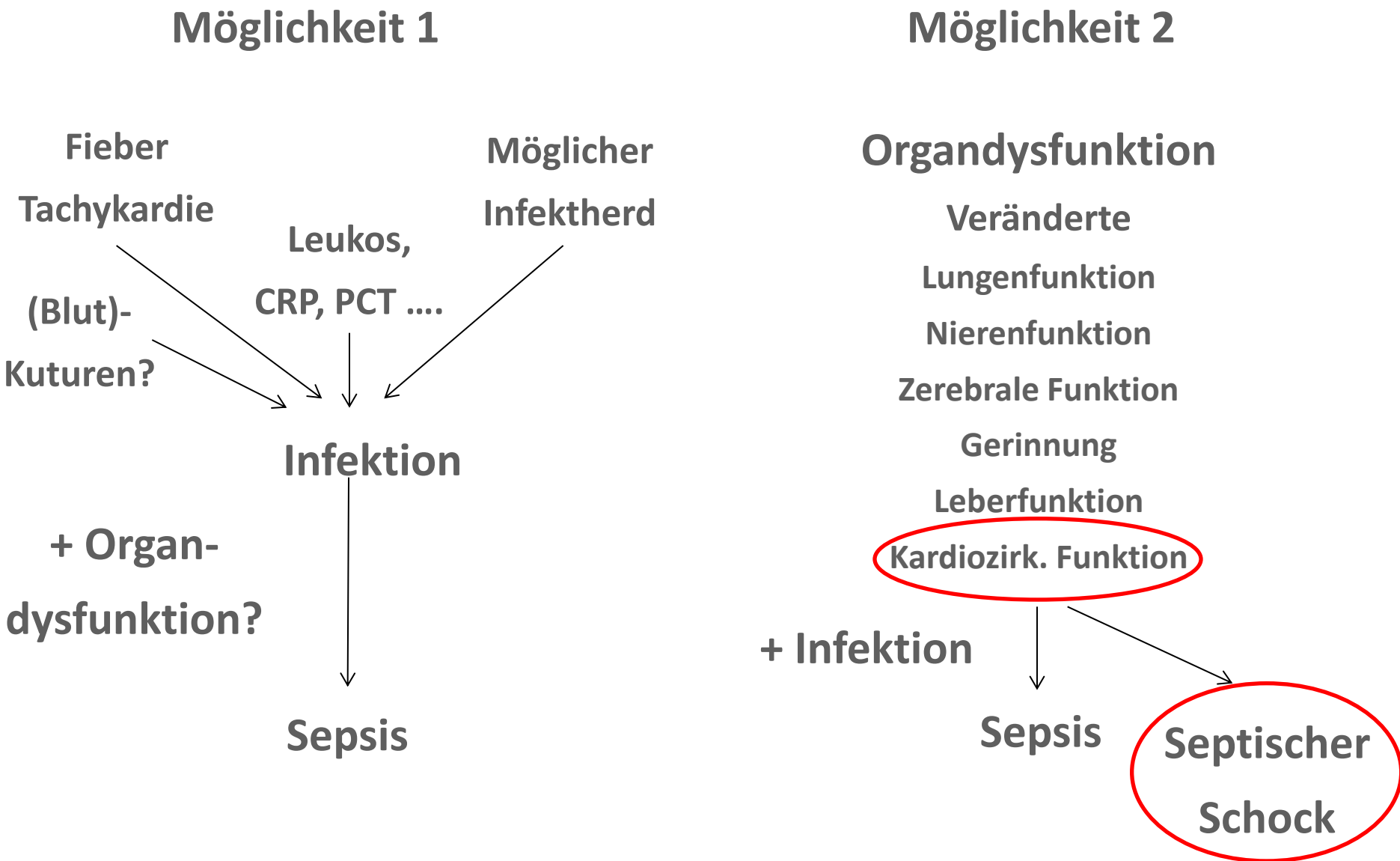
Sepsisdiagnosekriterien?



Lactate Measurements in Sepsis-Induced Tissue Hypoperfusion: Results From the Surviving Sepsis Campaign Database*

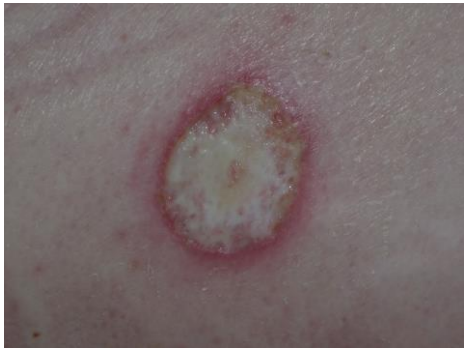
(*Crit Care Med* 2015; 43:567–573)

Brian Casserly, MD[1,3,4]; Gary S. Phillips, MAS[5]; Christa Schorr, RN, MSN[6]; R. Phillip Dellinger, MD[6]; Sean R. Townsend, MD[7]; Tiffany M. Osborn, MD, MPH[8]; Konrad Reinhart, MD[9]; Narendran Selvakumar, MD[4]; Mitchell M. Levy, MD[2,3]

Lactate Group (mmol/L)	Compliant Lactate Measured ≤ 6 hr			
	No Hypotension		Hypotension	
	Total, *n* (Died *n*/%)	OR[a] (95% CI) [*p*]	Total, *n* (Died *n*/%)	OR[a] (95% CI) [*p*]
≤ 2 (referent)	1,302 (301/23.1)	1.00	5,158 (1,423/27.6)	1.00
> 2 to ≤ 3	1,009 (242/24.0)	1.04 (0.87–1.24) [0.661]	3,241 (991/30.6)	1.16 (1.05–1.27) [0.002]
> 3 to ≤ 4	693 (158/22.8)	0.99 (0.80–1.21) [0.891]	2,274 (718/31.6)	1.21 (1.09–1.35) [< 0.001]
> 4	996 (289/29.0)	1.38 (1.16–1.65) [< 0.001]	5,272 (2,344/44.5)	2.10 (1.93–2.27) [< 0.001]

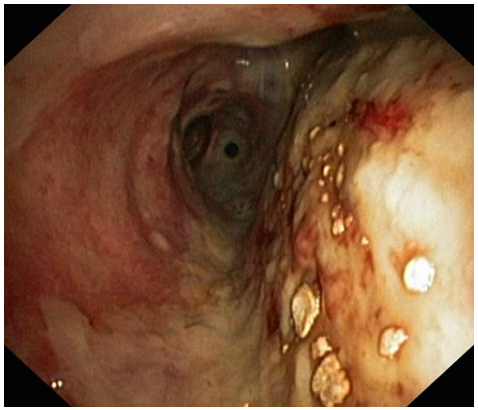
highly associated with in-hospital mortality. However, only patients who presented with lactate values greater than 4 mmol/L, with and without hypotension, are significantly associated with in-hospital mortality and is associated with a significantly higher risk than intermediate levels (2–3 and 3–4 mmol/L). This supports the use of

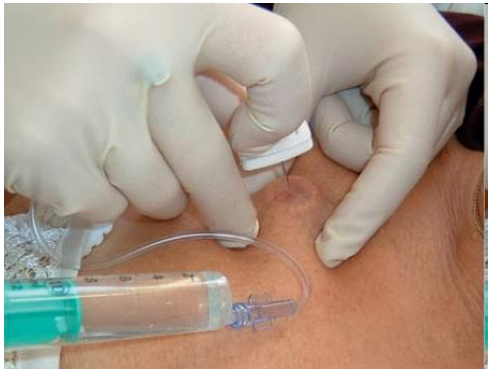
Vorgehen zur Focussuche

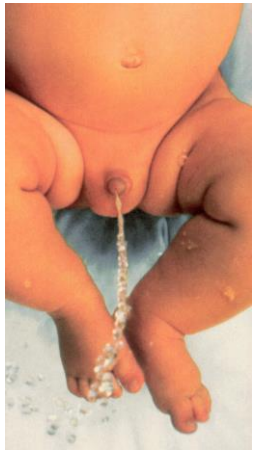


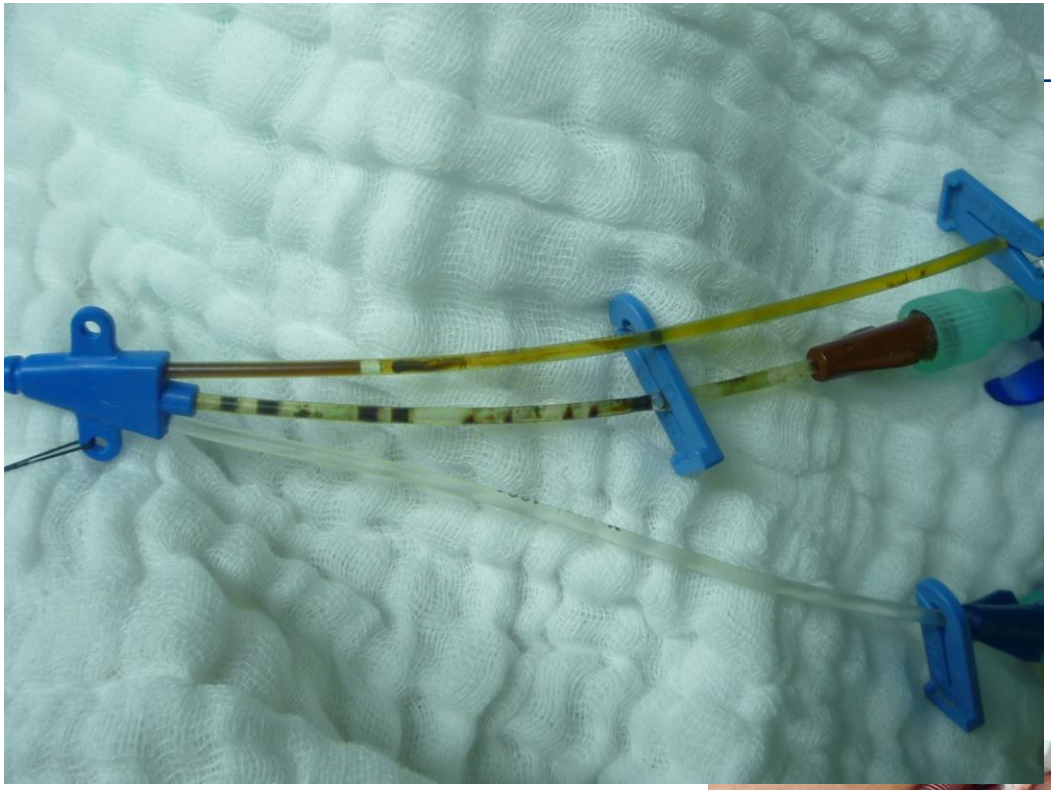
- Mikrobiologische Diagnostik

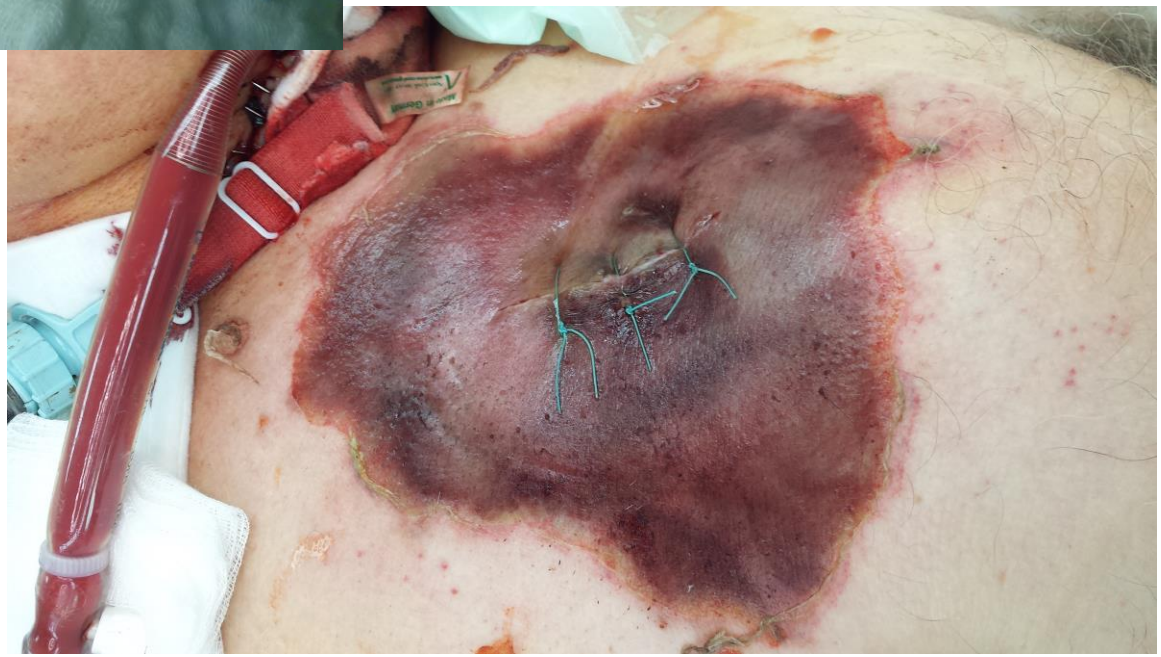
- Atemwege
- Wunden Drainagen
- einliegende Katheter
- Urin
- Blut



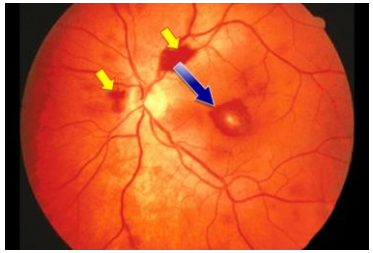




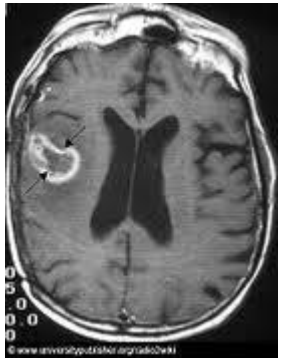




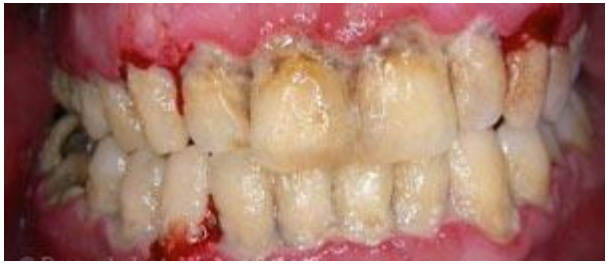
Weitere Foci



- Auge
- Mittelohr und Nasennebenhöhlen

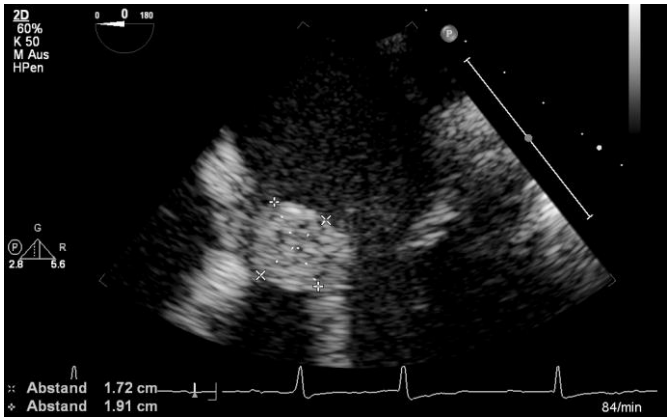


- Zähne



- ZNS
- Endokard und Herzklappen
- Knochen

- Darm



Surviving Sepsis Campaign guidelines for management of severe sepsis and septic shock

R. Phillip Dellinger, Thierry Calandra, M

Special Articles

Surviving Sepsis Campaign: International Guidelines for Management of Severe Sepsis and Septic Shock: 2012

R. Phillip Dellinger, MD[1]; Mitchell M. Levy, MD[2]; Andrew Rhodes, MB BS[3]; Djillali Annane, MD[4]; Herwig Gerlach, MD, PhD[5]; Steven M. Opal, MD[6]; Jonathan E. Sevransky, MD[7]; Charles L. Sprung, MD[8]; Ivor S. Douglas, MD[9]; Roman Jaeschke, MD[10]; Tiffany M. Osborn, MD, MPH[11]; Mark E. Nunnally, MD[12]; Sean R. Townsend, MD[13]; Konrad Reinhart, MD[14]; Ruth M. Kleinpell, PhD, RN-CS[15]; Derek C. Angus, MD, MPH[16]; Clifford S. Deutschman, MD, MS[17]; Flavia R. Machado, MD, PhD[18]; Gordon D. Rubenfeld, MD[19]; Steven A. Webb, MB BS, PhD[20]; Richard J. Beale, MB BS[21]; Jean-Louis Vincent, MD, PhD[22]; Rui Moreno, MD, PhD[23]; and the Surviving Sepsis Campaign Guidelines Committee including the Pediatric Subgroup*

AWM

...gement

...: 2008

...vision der S2k-Leitlinien der Deutschen Sepsis-Gesellschaft e.V. (DSG) und der Deutschen Interdisziplinären Vereinigung für Intensiv- und Notfallmedizin (DIVI)

K. Reinhart (1), F. M. Brunkhorst
Gründling (4), G. Kreymann (5), P.
Hellmann (9), C. Peckelsen (10), C.
Rossaint (14), F. Stüber (11), N. Weiler (16), T. Wel

Intensivmed 2010 · 47:185–207

Therapie der Sepsis

Herdsanierung

Eine spezifische anatomische Diagnose der Infektion, für die eine Herdsanierung in Betracht kommt, soll so schnell wie möglich gesucht und diagnostiziert oder ausgeschlossen werden, und eine Intervention zur Herdsanierung innerhalb der ersten 12 Stunden nach der Diagnose, sofern machbar, durchgeführt werden.

RP Dellinger et al.

***Crit Care Med* 41, 580-637 (2013)**

Critical Care Medicine

In einer retrospektiven Arbeit an 106 Intensivpatienten zeigte sich, dass bei Patienten mit septischem Schock (n=43) die Zeit von der Diagnose zur operativen Herdsanierung von > 14 h bei nekrotisierender Weichgewebsinfektion unabhängig mit der Krankenhaussterblichkeit assoziiert war.

A Boyer et al.

***Int Care Med* 35, 847-853 (2009)**

INTENSIVE CARE MEDICINE

Impact of compliance with infection management guidelines on outcome in patients with severe sepsis: a prospective observational multi-center study

Bloos *et al. Critical Care* 2014, **18**:R42
http://ccforum.com/content/18/2/R42

Methods: In a prospective observational multi-center cohort study in 44 German ICUs, we studied 1,011 patients with severe sepsis or septic shock regarding times to AT, source control, and adequacy of AT. Primary outcome was 28-day mortality.

Results: (...) Time to AT was significantly longer in ICU and hospital non-survivors; no linear relationship was found between time to AT and 28-day mortality. Regardless of timing, 28-day mortality rate was lower in patients with adequate than non-adequate AT (30.3% versus 40.9%, $P < 0.001$).

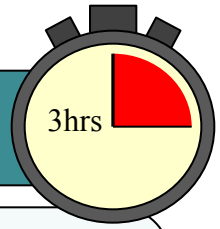
Table 3 Time to antimicrobial therapy and source control according to survival

	Survivors	Non-Survivors	p-value
Time to antimicrobial therapy (hrs)			
28 days survival	2.0 (0.6 – 5.6)	2.5 (1.0 – 6.6)	0.112
	N = 659	N = 352	
ICU survival	2.0 (0.7 – 5.4)	2.8 (0.9 – 7.0)	0.023
	N = 667	N = 329	
Hospital survival	2.0 (0.6 – 5.1)	2.8 (0.9 – 7.0)	0.020
	N = 581	N = 329	
Time to source control (hrs)			
28 days survival	2.0 (−0.5 – 10.1)	5.7 (0.4 – 18.0)	0.004
	N = 286	N = 139	
ICU survival	2.0 (−0.6 – 9.1)	6.0 (0.5 – 19.9)	<0.001
	N = 286	N = 132	
Hospital survival	2.0 (−0.5 – 9.3)	5.5 (0.4 – 18.9)	0.001
	N = 249	N = 166	

Data are shown as median and interquartile range. ICU: intensive care unit.

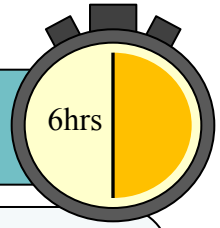
Surviving Sepsis Campaign Bundles

3-Hour Bundle



- measure lactate level
- obtain blood cultures prior to administration of antibiotics
- administer broad spectrum antibiotics
- administer 30mL/kg crystalloid for hypotension or lactate ≥4mmol/L

6-Hour Bundle



- apply vasopressors (for hypotension that does not respond to initial fluid resuscitation) to maintain MAP ≥65mmHg
- In the event of persistant arterial hypotension despite volume resuscitation (septic shock) or initial lactate ≥4mmol/L:
  - measure CVP
  - Measure $Scvo_2$
- remeasure lactate if initial lactate was elevated

Antiinfektive Therapie

Die Applikation von effektiven antimikrobiellen Substanzen innerhalb der ersten Stunde nach Erkennen eines septischen Schocks und einer schweren Sepsis ohne septischen Schock ist ein Therapieziel.

RP Dellinger et al.
Crit Care Med 41, 580-637 (2013)

Critical Care Medicine
Society of Critical Care Medicine

New SCC recommendations

4b. Empiric combination therapy should not be administered for more than 3–5 days. De-escalation to the most appropriate single therapy should be performed as soon as the susceptibility profile is known (grade 2B).

5. Duration of therapy typically 7–10 days; longer courses may be appropriate in patients who have a slow clinical response, undrainable foci of infection, bacteremia with *S. aureus;* some fungal and viral infections or immunologic deficiencies, including neutropenia (grade 2C).

6. Antiviral therapy initiated as early as possible in patients with severe sepsis or septic shock of viral origin (grade 2C).

7. Antimicrobial agents should not be used in patients with severe inflammatory states determined to be of noninfectious cause (UG).

Dellinger RP et al. CCM 2013

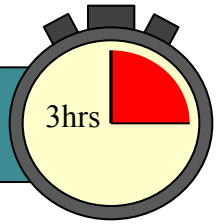
Wie führe ich beim Patienten mit Sepsis eine antibakterielle Therapie durch?

Tab. 3a: Die kalkulierte antibiotische Therapie bei nosokomialer Sepsis bei *bekanntem Infektionsherd (MRSA siehe 3b)* (mod. nach [3])

	Atemwege	Harntrakt	Darm/Gynäkologische Organe	Haut/ Weichteil	Katheter-assoziiert
ANTIBIOSE	• **Cephalosporin 3b/4** • **Acylaminopenicillin/BLI** • **Carbapenem 1** Je + Fluorchinolon 2/3 oder + Fosfomycin	• **Fluorchinolon 2/3** • **Cephalosporin 3a/3b/4** • **Acylaminopenicillin/BLI** • **Carbapenem 1**	• **Acylaminopenicillin/BLI** • **Cephalosporin 3b/4** + Metronidazol/ + Aminopenicillin (bei Gallenwegen) • **Flurchinolon 2/3** + Metronidazol/ + Aminopenicillin (bei Gallenwegen) • **Carbapenem 1** **+/- Glycycyclin**	• **Cephalosporin 3b/4** + Clindamycin • **Acylaminopenicillin/BLI** +/- Clindamycin • **Flurchinolon 2/3** + Cephalosporin 2 oder + Clindamycin • **Carbapenem 1** + Clindamycin	• **Acylaminopenicillin/BLI** oder • **Cephalosporin 3b/4** oder • **Carbapenem 1** je **+/- Vancomycin** oder **+/- Daptomycin**

Cephalosporine: Gruppe 1: Cefazolin; Gruppe 2: Cefuroxim, Cefotiam; Gruppe 3a: Cefotaxim, Ceftriaxon; Gruppe 3b: Ceftazidim; Gruppe 4: Cefepim
Carbapeneme: Gruppe 1: Doripenem, Imipenem/Cilastatin, Meropenem; Guppe 2: Ertapenem

3-Hour Bundle



measure lactate level

administer 30mL/kg crystalloid for hypotension or lactate ≥4mmol/L

obtain blood cultures prior to administration of antibiotics

administer broad spectrum antibiotics

Bernhard *et al. Critical Care* 2014, **18**:671
http://ccforum.com/content/18/6/671

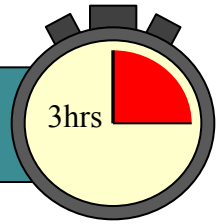
CRITICAL CARE

COMMENTARY

The early antibiotic therapy in septic patients - milestone or sticking point?

Michael Bernhard[1*], Christoph Lichtenstern[2], Christian Eckmann[3] and Markus A Weigand[2]

3-Hour Bundle



measure lactate level

administer 30mL/kg crystalloid for hypotension or lactate ≥4mmol/L

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administer broad spectrum antibiotics

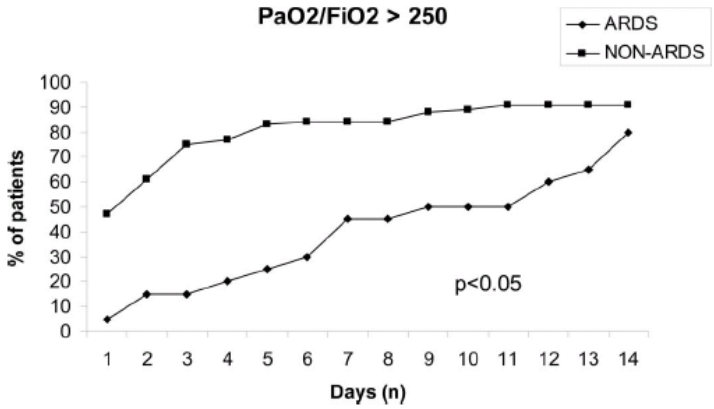
Zeitdauer bis zur Antibiotikagabe

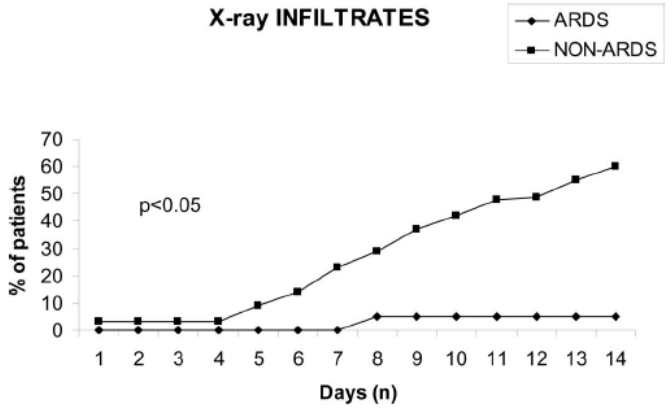
	wichtig		unwichtig		
	Kumar *et al.* *Crit Care Med* (2006)	**Ferrer *et al.*** *Crit Care Med* (2014)	**Puskarich *et al.*** *Crit Care Med (2011)*	**Bloos *et al.*** *Crit Care* (2014)	**Hranjec *et al.*** *Lancet Infect Dis* (2012)
Study design	Retrospective multicenter cohort study	Retrospective analysis of prospective collected dataset multicenter	Prospective preplanned analysis of a multicenter randomized clinical trial	Prospective multicenter cohort study	Prospective quasi-experimental, before-and-after observational study single center
Setting	ICU septic shock	ICU mixed	ED septic shock	ICU	ICU-auired infection
Patients	2,731	17,993	291	1,011	484

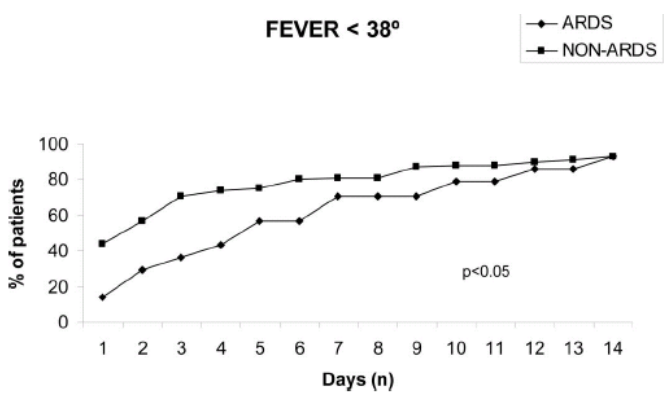
Bernhard *et al. Critical Care* 2014, **18**:671
http://ccforum.com/content/18/6/671

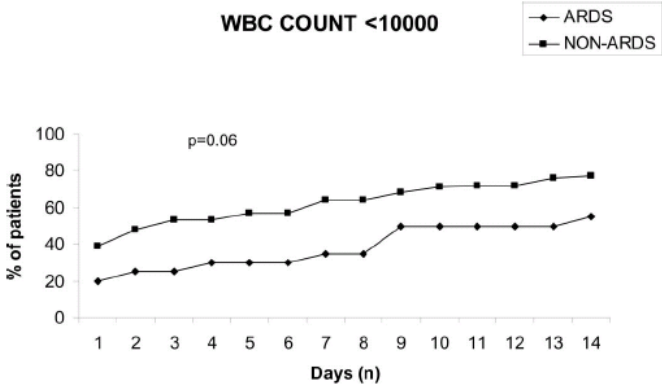
Ansprechen auf die Therapie

Vidaur L et al. CCM 2005; 33:1248-53









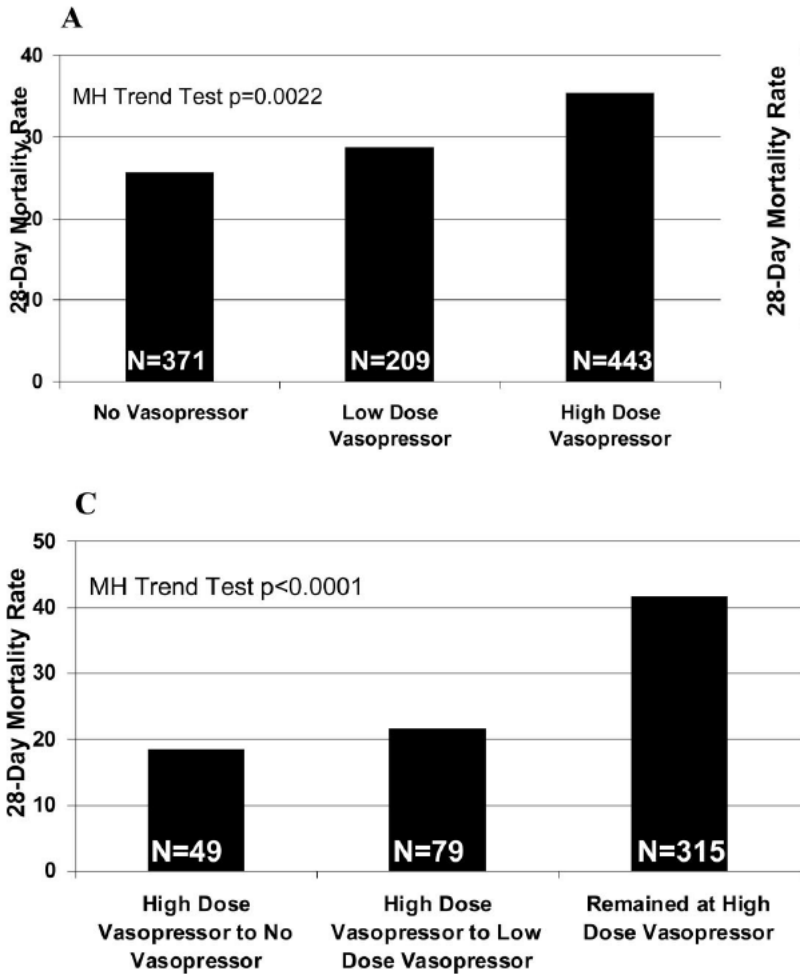
Wenn sich die Organdysfunktion nicht bessert:

Herdsanierung adäquat?, atypische Bakterien, ESBL, MRSA, VRE, Pilze?
Pseudomembranöse Colitis? Drug Fieber?

Early changes in organ function predict eventual survival in severe sepsis*

Crit Care Med 2005 Vol. 33, No. 10

Mitchell M. Levy, MD, FCCM; William L. Macias, MD, PhD; Jean-Louis Vincent, MD, PhD, FCCM; James A. Russell, MD; Eliezer Silva, MD, PhD; Benjamin Trzaskoma, MS; Mark D. Williams, MD



Und das Laktat muss fallen

Early Goal Directed Therapy

Emanuel Rivers

- CVP > 8-12 mmHg
- MAP ≥ 65 mmHg
- Urine output ≥ 0.5 ml/kg/h
- Superior vena cava oxygen saturation ($ScVO_2$) or mixed venous oxygen saturation (SVO_2) 70% or 65%, respectively (grade 1C)

Emanuel Rivers et al.
N Engl J Med 345:1368-1377 (2001)

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 MAY 1, 2014 VOL. 370 NO. 18

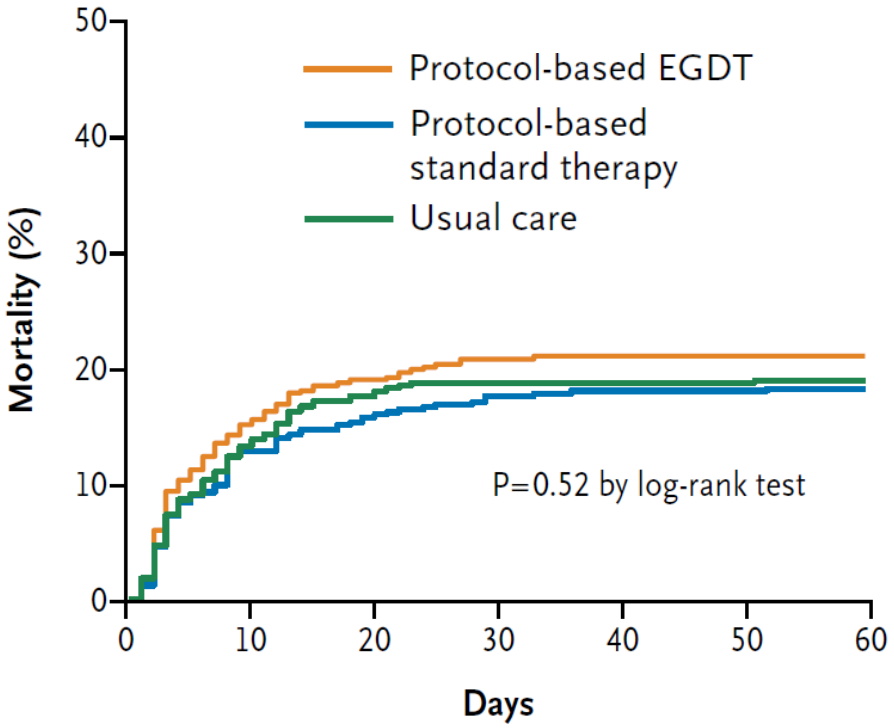
A Randomized Trial of Protocol-Based Care for Early Septic Shock

The ProCESS Investigators*

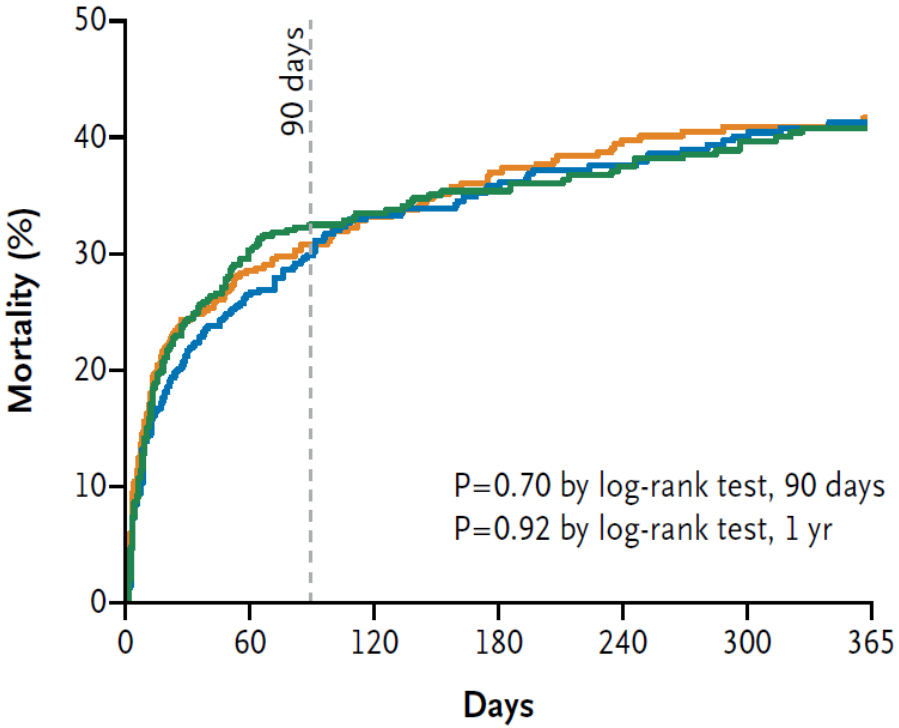
METHODS

In 31 emergency departments in the United States, we randomly assigned patients with septic shock to one of three groups for 6 hours of resuscitation: protocol-based EGDT; protocol-based standard therapy that did not require the placement of a central venous catheter, administration of inotropes, or blood transfusions; or usual care. The primary end point was 60-day in-hospital mortality. We tested sequen-

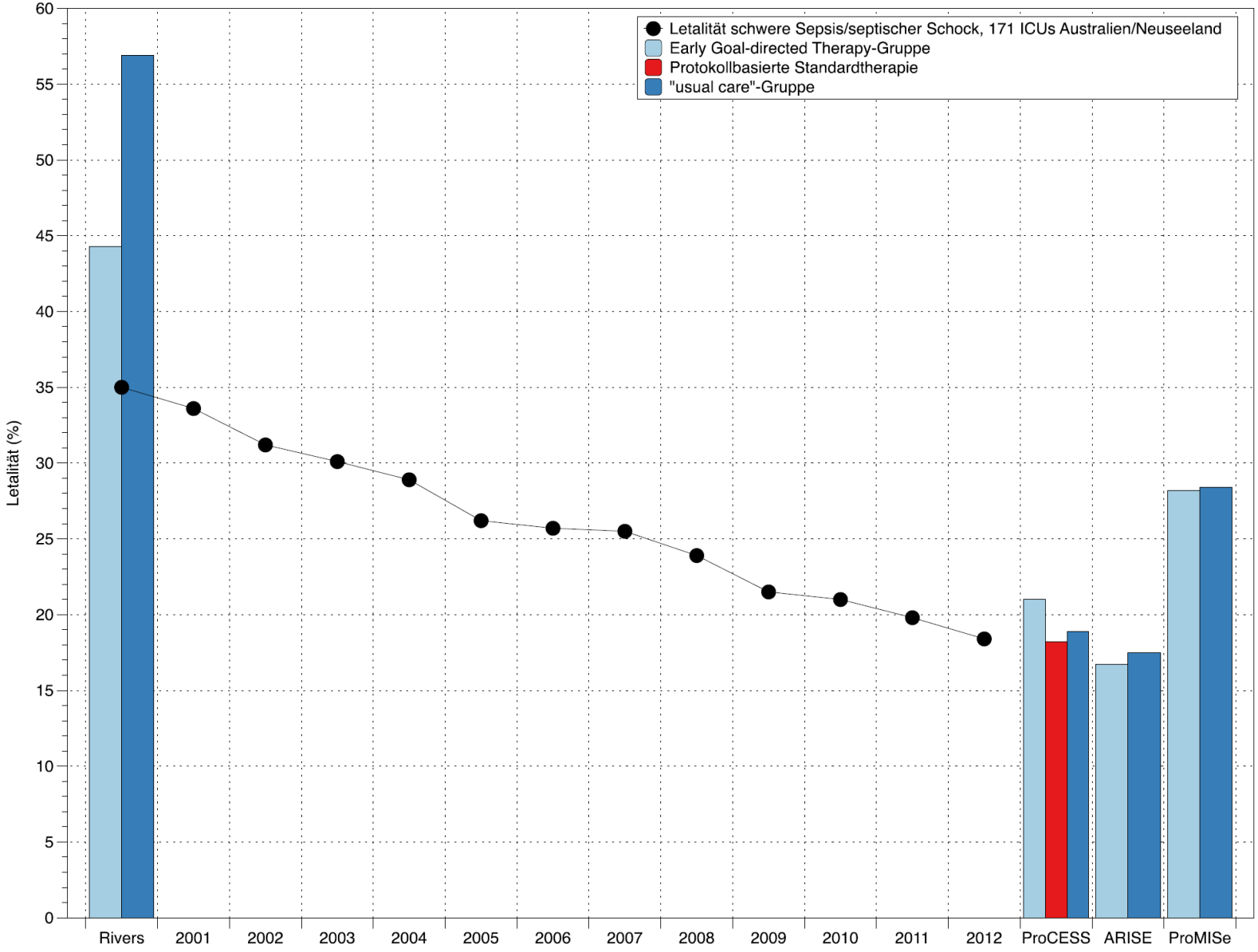
Cumulative in-Hospital Mortality to 60 days



Cumulative Mortality to 1 Yr



11. Kaukonen KM, Bailey M, Suzuski S, Pilcher D, Bellomo R (2014) Mortality related to severe sepsis and septic shock among critically ill patients in Australia and New Zealand, 2000-2012. JAMA 311: 1308-1316



	Rivers et al. [20]		**ARISE [19]**		**ProCESS [24]**			**ProMISe [18]**	
Studienarme	EGDT (n=130)	UC (n=133)	EGDT (n=792)	UC (n=796)	EGDT (n=439)	ST (n=446)	UC (n=456)	EGDT (n=623)	UC (n=620)
Volumen (ml), 0-6h	4981 ±2984	3499 ±2438	1964 ±1415	1713 ±1401	2805 ±1957	3285 ±1743	2279 ±1881	2226 ±1443	2022 ±1271
Vasopressoren (%), 0-6 h	27,4	30,3	66,6	57,8	54,9	52,2	44,1	53,3	46,6
Erythrozytengabe (%), 0-6h	64,1	18,5	13,6	7,0	14,4	8,3	7,5	8,8	3,8
Dobutamin (%), 0-6h	13,7	0,8	15,4	2,6	8,0	1,1	0,9	18,1	3,8

- Die **klinische Untersuchung** von Patienten in der Notaufnahme muss die Erkennung von Mikrozirkulationsstörungen beinhalten.
- Die **Messung der Vitalfunktionen** (prä- und innerklinisch: Blutdruck, Herzfrequenz, pulsoxymetrische Sauerstoffsättigung, Atemfrequenz, Temperatur) und die **Laktatbestimmung** (innerklinisch) sind wesentliche Eckpfeiler im Rahmen der Früherkennung einer Sepsis.
- Eine **adäquate Volumentherapie** bei der initialen Sepsisbehandlung ist von entscheidender Bedeutung, wobei in der Initialphase zwei großlumige periphervenöse Gefäßzugänge ausreichend sind und häufig kein zentraler Venenzugang notwendig ist.
- Neben der **Identifikation des Infektfokus** ist eine zeitnahe Probenasservierung (z.B. Blut- und Urinkulturen, Trachealsekret) notwendig. Zudem sollte möglichst eine zeitnahe **Fokussanierung** (Source Control, z.B. operative Intervention) erfolgen.
- Eine **frühzeitige Antibiotikatherapie** nach den o.g. Maßnahmen erscheint weiterhin im Rahmen der Sepsistherapie notwendig und sollte bei Sepsis, schwerer Sepsis und septischen Schock noch in der Zentralen Notaufnahme erfolgen.

ORIGINAL ARTICLE

High versus Low Blood-Pressure Target in Patients with Septic Shock

Pierre Asfar, M.D., Ph.D., Ferhat Meziani, M.D., Ph.D., Jean-François Hamel, M.D.,

This article was published on March 18, 2014, at NEJM.org.

METHODS

In a multicenter, open-label trial, we randomly assigned 776 patients with septic shock to undergo resuscitation with a mean arterial pressure target of either 80 to 85 mm Hg (high-target group) or 65 to 70 mm Hg (low-target group). The primary end point was mortality at day 28.

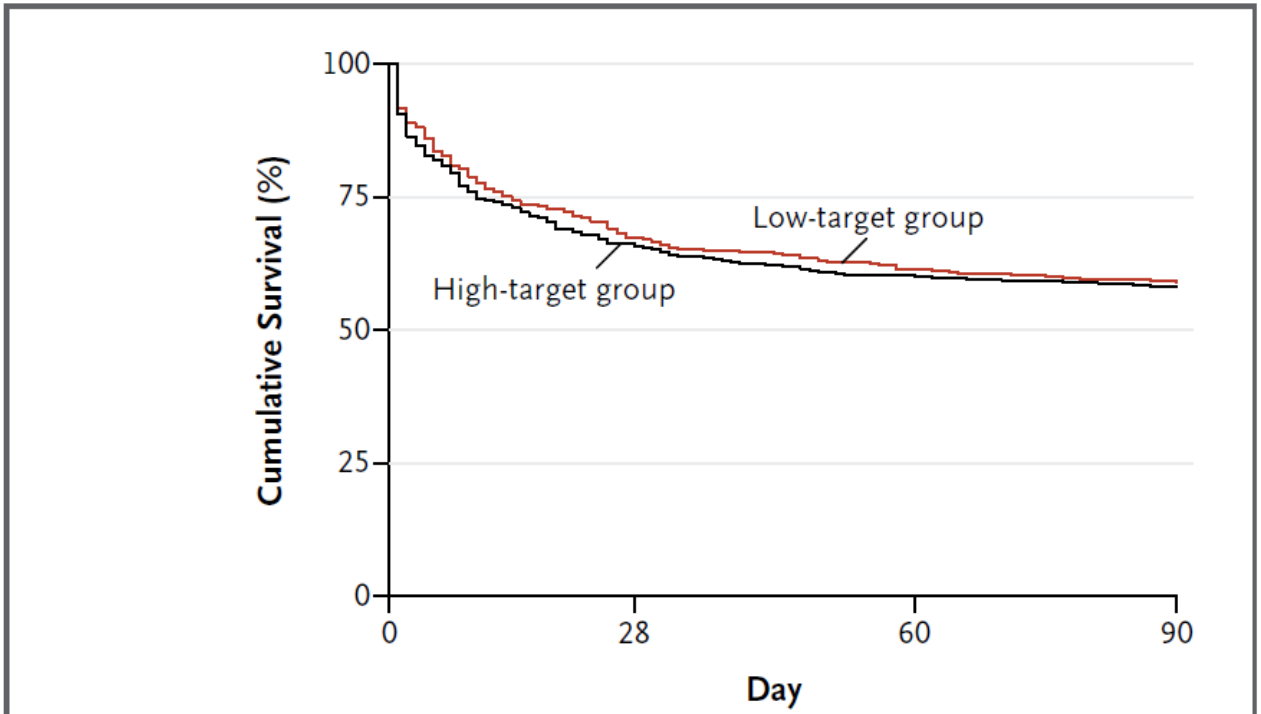


Figure 3. Kaplan–Meier Curves for Cumulative Survival.

(74 events [19.1%] and 69 events [17.8%], respectively; P=0.64). However, the incidence of newly diagnosed atrial fibrillation was higher in the high-target group than in the low-target group. Among patients with chronic hypertension, those in the high-target group required less renal-replacement therapy than did those in the low-target group, but such therapy was not associated with a difference in mortality.

New SSC recommendations

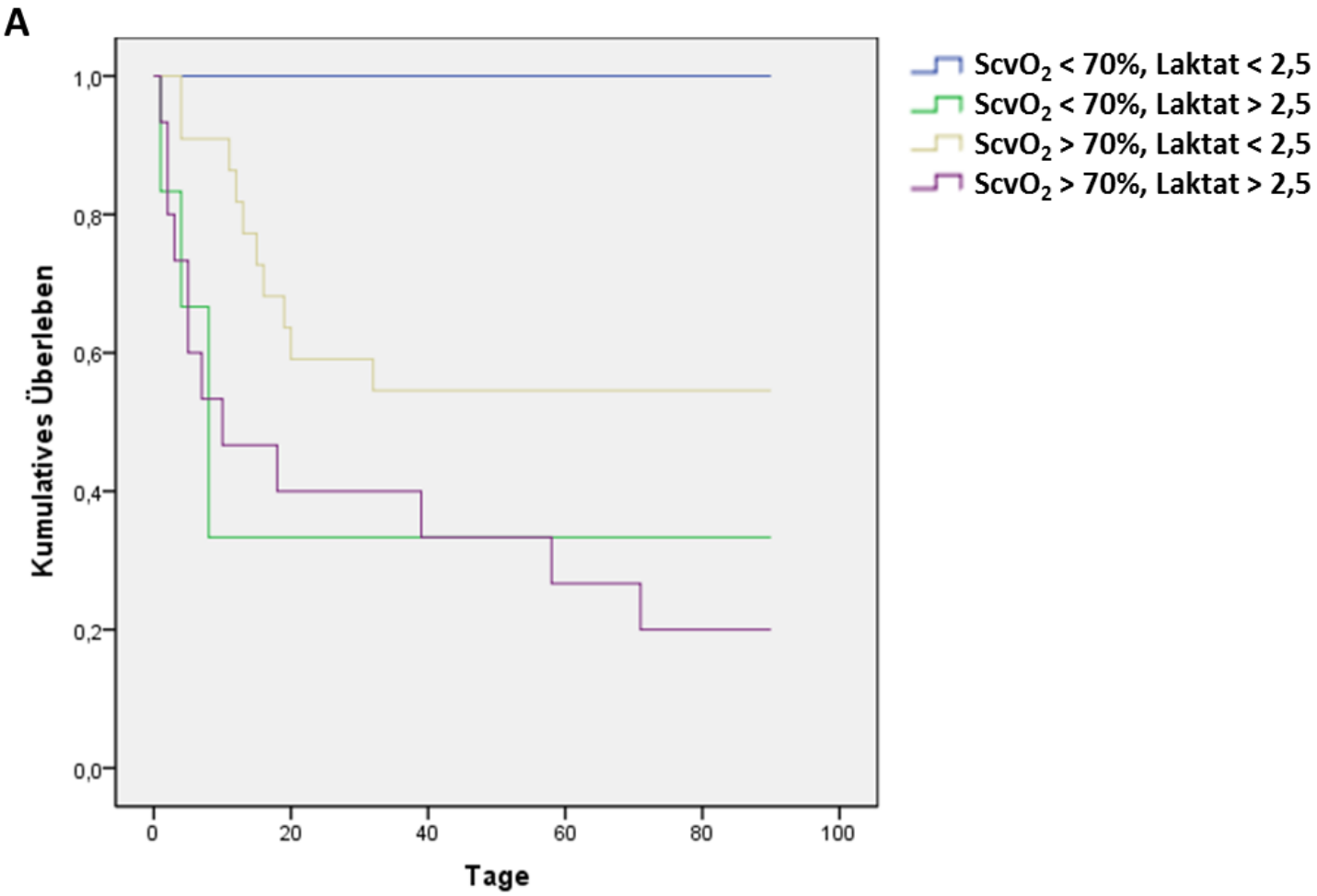
We suggest targeting resuscitation to normalize lactate in patients with elevated lactate levels as a marker of tissue hypoperfusion

(grade 2C)

RP Dellinger et al.
Crit Care Med 41, 580-637 (2013)

Critical Care Medicine
Society of Critical Care Medicine

EGDT heute: Zielparameter $S_{cv}O_2$?



Early goal-directed therapy in the management of severe sepsis or septic shock in adults: a meta-analysis of randomized controlled trials

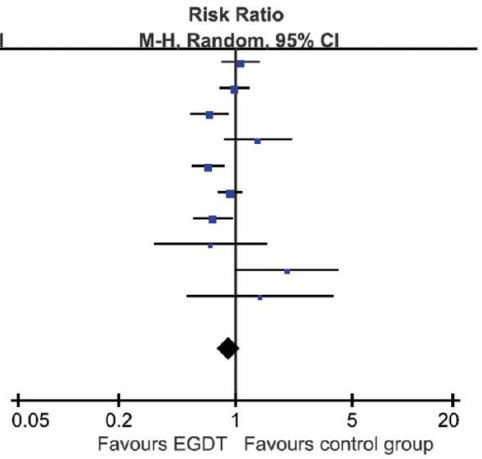
Ling Zhang[1], Guijun Zhu[2], Li Han[3] and Ping Fu[4*]

Overall mortality

1. EGDT vs. Control group

Study or Subgroup	EGDT Events	EGDT Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
Andrews 2014	35	49	36	54	12.9%	1.07 [0.83, 1.39]
ARISE 2014	147	792	150	796	14.7%	0.98 [0.80, 1.21]
Jing 2010	57	159	76	148	12.8%	0.70 [0.54, 0.91]
Jones 2010	34	150	25	150	7.4%	1.36 [0.86, 2.16]
Lin 2006	53	108	83	116	14.1%	0.69 [0.55, 0.86]
ProCESS 2014	257	820	139	412	15.9%	0.93 [0.78, 1.10]
Rivers 2001	50	130	70	133	12.5%	0.73 [0.56, 0.96]
Wang 2006	6	16	9	17	3.5%	0.71 [0.33, 1.54]
Wang 2014	17	31	7	26	4.0%	2.04 [1.00, 4.14]
Yu 2013	7	25	5	25	2.2%	1.40 [0.51, 3.82]
Total (95% CI)		**2280**		**1877**	**100.0%**	**0.91 [0.77, 1.07]**
Total events	663		600			

Heterogeneity: Tau² = 0.03; Chi² = 23.46, df = 9 (P = 0.005); I² = 62%
Test for overall effect: Z = 1.18 (P = 0.24)



4. Standard EGDT vs. Early lactate clearance

Study or Subgroup	Standard EGDT Events	Standard EGDT Total	Early lactate clearance Events	Early lactate clearance Total	Weight	Risk Ratio M-H, Random, 95% CI
Jones 2010	34	150	25	150	60.9%	1.36 [0.86, 2.16]
Wang 2014	17	31	7	26	26.1%	2.04 [1.00, 4.14]
Yu 2013	7	25	5	25	13.0%	1.40 [0.51, 3.82]
Total (95% CI)		**206**		**201**	**100.0%**	**1.52 [1.06, 2.18]**
Total events	58		37			

Heterogeneity: Tau² = 0.00; Chi² = 0.90, df = 2 (P = 0.64); I² = 0%
Test for overall effect: Z = 2.25 (P = 0.02)

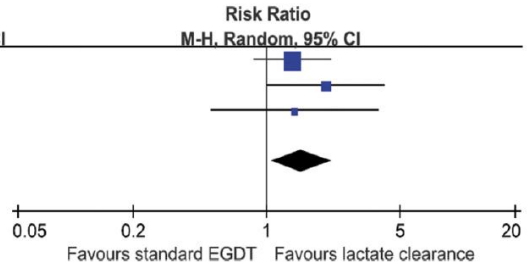


Figure 3 Forest plot for overall mortality. The analysis was stratified by study design. Risk ratio (RR) < 1.0 favors EGDT. Abbreviations: CI, confidence interval; M-H, Mantel-Haenszel.

AWMF-Register-Nr.: 001/020

Deutsche Gesellschaft für Anästhesiologie & Intensivmedizin

S3-Leitlinie

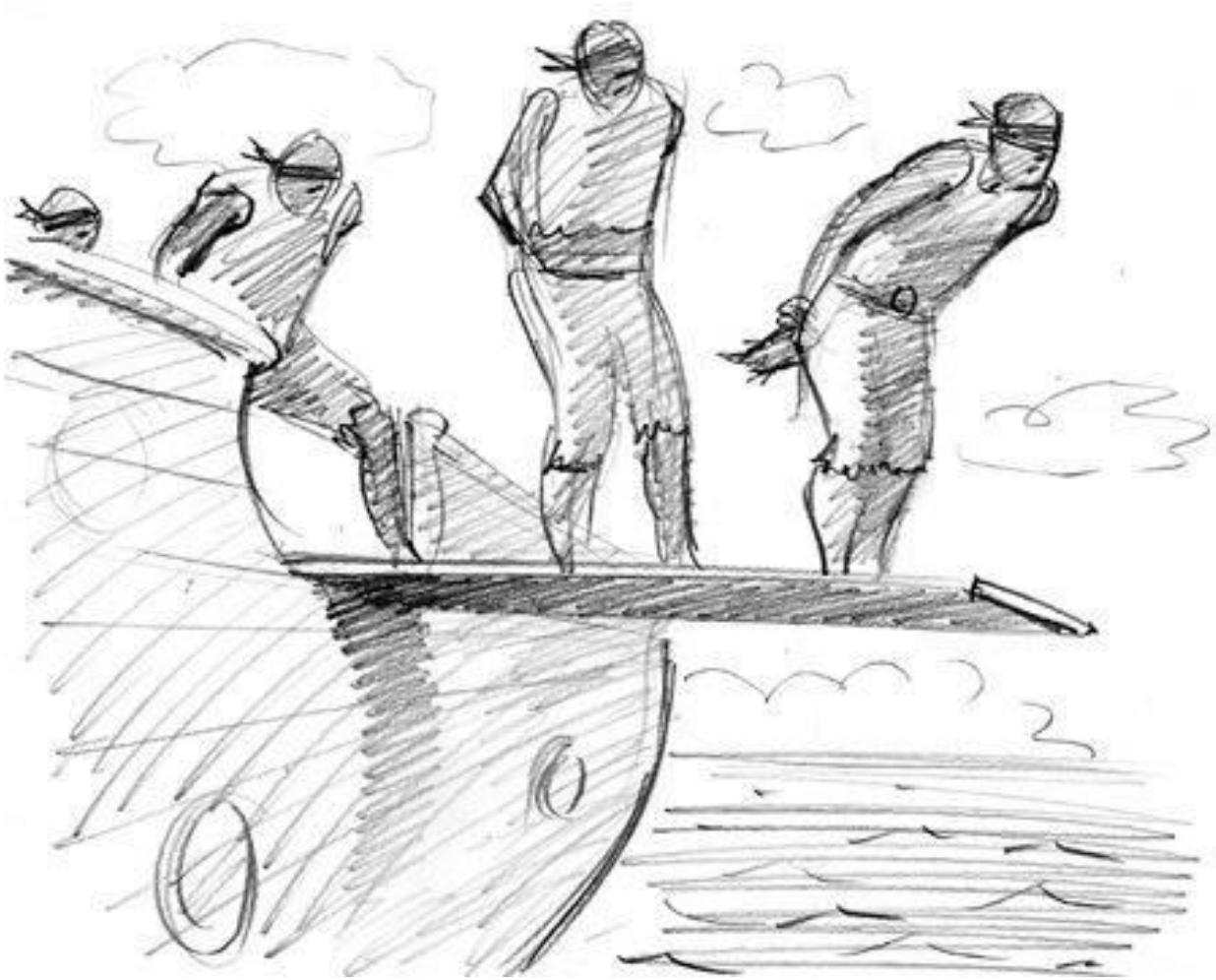
Intravasale Volumentherapie beim Erwachsenen

Empfehlung 1-3[1]	**GoR**
Für die Diagnose eines Volumenmangels bei spontan atmenden sowie bei beatmeten Patienten soll der ZVD sowohl bei peri-operativen als auch bei intensivmedizinischen Patienten nicht verwendet werden.	A

.[1] Diese Empfehlung wurde durch die Deutsche Sepsisgesellschaft (DSG) im Rahmen der externen Begutachtung wie folgt kommentiert: ***Die DSG kann dieser Empfehlung nicht zustimmen, weil Prognosestudien hierzu nicht vorliegen und die Balance zwischen dem Nutzen und Risiko dieser Grad A-Empfehlung nicht ausgewogen ist („undesirable probably outweigh desirable“).***

Unter folgendem Link kommen Sie indirekt auf die Leitlinien:
Link: http://www.awmf.org/leitlinien/leitlinien-suche.html#result-list

Der Weg des ZVD?



http://images.sodahead.com/profiles/0/0/1/8/2/8/2/6/7/walk-the-plank-13376581192.jpeg

Gründe, den ZVD also *doch* zu messen:

- ZVD als **Sicherheitsparameter**:
  - Vermeidung einer Überinfusion, insbesondere bei chronisch gestauten Herzen
- Informationsgewinn bei **(Verlaufs)Beobachtung**:
  - Akuter Anstieg: Rechtsherzversagen? Perikardtamponade?
  - Zentralvenöse Druckkurve: Hinweis auf Trikuspidalinsuffizienz?
- **Limitationen dynamischer Vorlastparameter**:
  - zur Messung der Volumenreagibilität
  - fragliche Validität in der Frühphase der Sepsis

Intensive Care Med
DOI 10.1007/s00134-014-3638-4

ORIGINAL

Zhongheng Zhang
Hongying Ni
Zhixian Qian

Received: 26 September 2014
Accepted: 28 December 2014

Effectiveness of treatment based on PiCCO parameters in critically ill patients with septic shock and/or acute respiratory distress syndrome: a randomized controlled trial

Abstract *Purpose:* To compare treatment based on either PiCCO-derived physiological values or central venous pressure (CVP) monitoring, we performed a prospective randomized controlled trial with group sequential analysis.

Methods: Consecutive critically ill patients with septic shock and/or ARDS were included. The planned total sample size was 715. The primary outcome was 28-day mortality after randomization.

Intensive Care Med
DOI 10.1007/s00134-014-3638-4

ORIGINAL

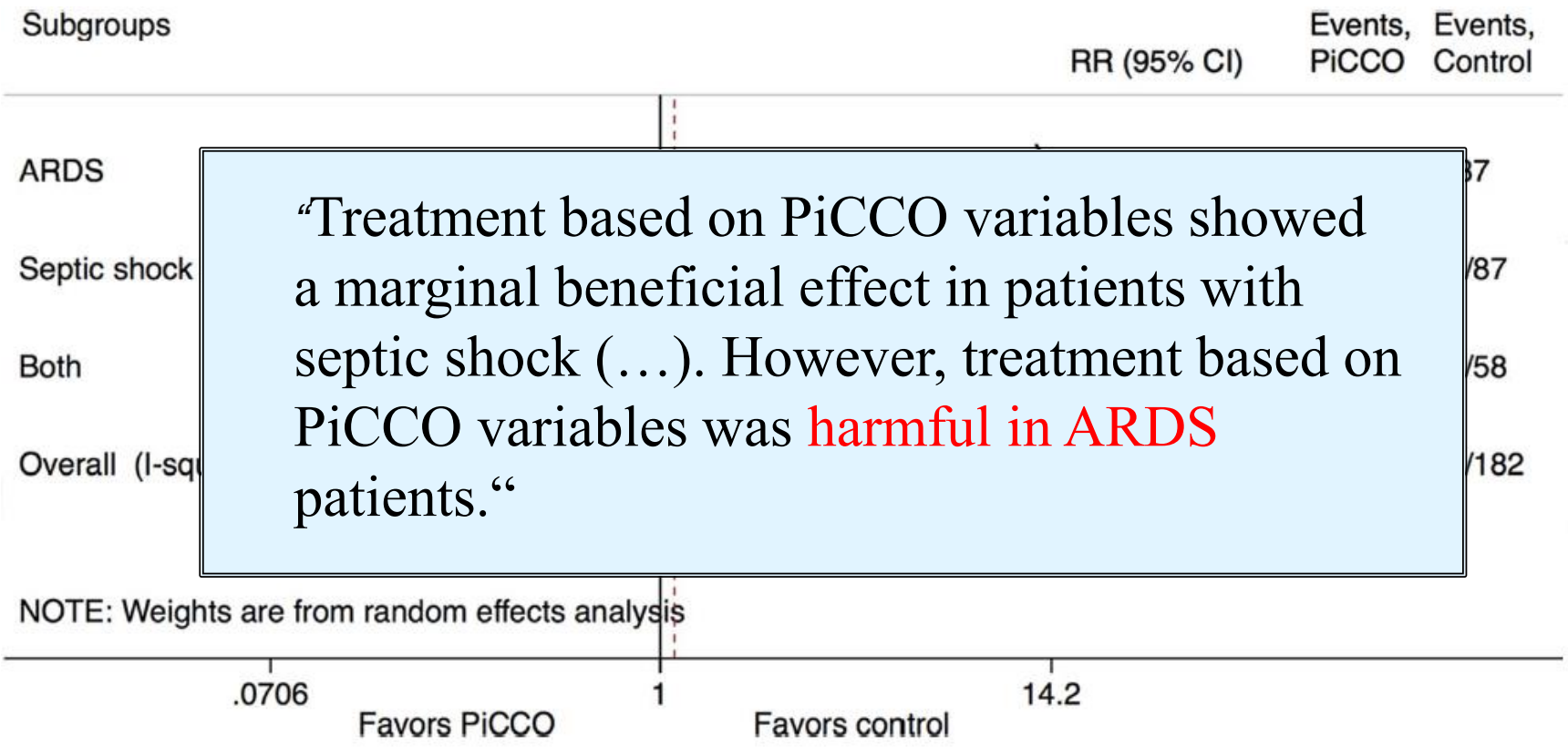
volume status assessed by using CVP (aiming to maintain CVP between 8 and 12 mmHg)

Outcome variables	PiCCO group (n = 168)	Control group (n = 182)	P value
Primary outcome			
28-day mortality	83 (49.4)	90 (49.5)	0.993
Secondary outcomes			
Maximum SOFA	13 (10–15)	12 (9–14)	0.023
14-day mortality	68 (40.5)	75 (41.2)	0.889
Days on vasopressor	4 (2–6)	3 (2–6.5)	0.852
Days on MV	6 (3–12)	5.5 (3–12)	0.897
Days on CRRT	4 (3–7)	4.5 (3–7)	0.586
Length of stay in ICU	9 (5–13)	7.5 (4–15)	0.598
Days free of vasopressor in 14 days	10 (0–12)	9 (0–12)	0.562
Days free of MV in 14 days	1 (0–10)	4 (0–12)	0.127
Days free of CRRT in 14 days	11 (3–14)	14 (4–14)	0.0038
Days free of vasopressor in 28 days	14.5 (0–25)	19 (0–26)	0.676
Days free of MV in 28 days	3 (0–24)	6 (0–25)	0.168
Days free of CRRT in 28 days	15.5 (3–28)	21 (4–28)	0.048

Patients without use of MV, CRRT, or vasopressor were treated as missing variable, instead of zero
MV mechanical ventilation, *ICU* intensive care unit, *IQR* interquartile range, *CRRT* continuous renal replacement therapy

Intensive Care Med
DOI 10.1007/s00134-014-3638-4

ORIGINAL



"Treatment based on PiCCO variables showed a marginal beneficial effect in patients with septic shock (…). However, treatment based on PiCCO variables was harmful in ARDS patients."

Surviving Sepsis Campaign

Updated Bundles in Response to New Evidence

TO BE COMPLETED WITHIN 6 HOURS OF TIME OF PRESENTATION:

5. Apply vasopressors (for hypotension that does not respond to initial fluid resuscitation) to maintain a mean arterial pressure (MAP) ≥65mmHg
6. In the event of persistent hypotension after initial fluid administration (MAP < 65 mm Hg) or if initial lactate was ≥4 mmol/L, re-assess volume status and tissue perfusion and document findings according to Table 1.
7. Re-measure lactate if initial lactate elevated.

TABLE 1

DOCUMENT REASSESSMENT OF VOLUME STATUS AND TISSUE PERFUSION WITH:

EITHER

- Repeat focused exam (after initial fluid resuscitation) by licensed independent practitioner including vital signs, cardiopulmonary, capillary refill, pulse, and skin findings.

OR TWO OF THE FOLLOWING:

- Measure CVP
- Measure $ScvO_2$
- Bedside cardiovascular ultrasound
- Dynamic assessment of fluid responsiveness with passive leg raise or fluid challenge

Of note, the 6-hour bundle has been updated; the 3-hour SSC bundle is not affected.

New SSC recommendations

- We recommend crystalloids be used as the initial fluid of choice in the resuscitation of severe sepsis and septic shock (grade 1B)

- We recommend against the use of hydroxyethyl starches (HES) for fluid resuscitation of severe sepsis and septic shock (grade 1B).

- We suggest the use of albumin in the fluid resuscitation of severe sepsis and septic shock when patients require substantial amounts of crystalloids (grade 2C)

RP Dellinger et al.
Crit Care Med 41, 580-637 (2013)
Critical Care Medicine
Society of Critical Care Medicine

	n	Population	Mortalität	Nierenversagen
SAFE *Albumin vs NaCl* *2006*	7000	Allgemeine ICU	kein Unterschied	kein Unterschied
VISEP *HES vs Ringer* *2008*	537	Schwere Sepsis	Trend zur *Zunahme HES* 90 Tage	Nachteil HES
6S *HES vs Ringer* *2012*	804	Schwere Sepsis	*Zunahme HES* 90 Tage	Nachteil HES
CHEST *HES vs NaCl* *2012*	7000	Allgemeine ICU	kein Unterschied	Nachteil HES
CRISTAL *Kolloid vs Kristalloid* *2013*	2857	Allgemeine ICU	*Zunahme Kristalloid* 90 Tage	kein Unterschied

Association Between the Choice of IV Crystalloid and In-Hospital Mortality Among Critically Ill Adults With Sepsis*

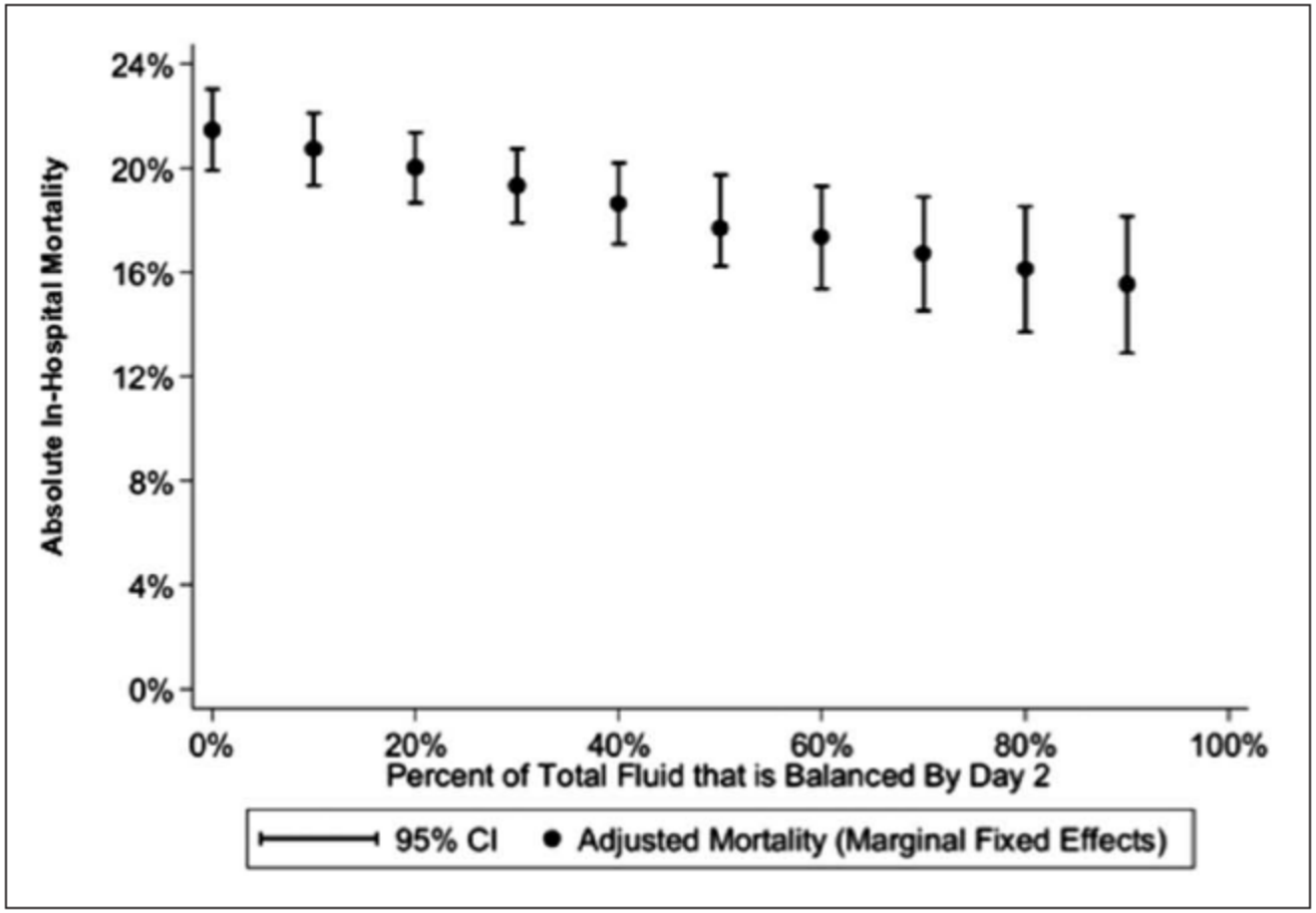
(*Crit Care Med* 2014; 42:1585–1591)

Karthik Raghunathan, MD, MPH[1,2]; Andrew Shaw, MB, FRCA, FFICM, FCCM[1]; Brian Nathanson, PhD[3]; Til Stürmer, MD, PhD[4]; Alan Brookhart, PhD[4]; Mihaela S. Stefan, MD[5]; Soko Setoguchi, MD, DrPH[6]; Chris Beadles, MD, PhD[2]; Peter K. Lindenauer, MD, MSc[7]

Design: A retrospective cohort study of patients admitted with sepsis, not undergoing any surgical procedures, and treated in an ICU by hospital day 2. We used propensity score matching to

Patients: A total of 53,448 patients with sepsis, treated with vasopressors and crystalloids in an ICU by hospital day 2 including 3,396 (6.4%) that received balanced fluids.

Association Between the Choice of IV Crystalloid and In-Hospital Mortality Among Critically Ill Adults With Sepsis*



Andrew D. Shaw
Karthik Raghunathan
Fred W. Peyerl
Sibyl H. Munson
Scott M. Paluszkiewicz
Carol R. Schermer

Association between intravenous chloride load during resuscitation and in-hospital mortality among patients with SIRS

Intensive Care Med
DOI 10.1007/s00134-014-3505-3

administered. *Methods:* We conducted a retrospective analysis of 109,836 patients ≥18 years old that met criteria for SIRS and received fluid resuscitation with crystalloids.

L). *Conclusions:* Among patients with SIRS, a fluid resuscitation strategy employing lower chloride loads was associated with lower in-hospital mortality. This association was inde-

„Blut ist ein ganz besonderer Saft“

(Mephistoteles, Faust I, Studierzimmer)

Johann Wolfgang von Goethe

ORIGINAL ARTICLE

Lower versus Higher Hemoglobin Threshold for Transfusion in Septic Shock

Lars B. Holst, M.D., Nicolai Haase, M.D., Ph.D., Jørn Wetterslev, M.D., Ph.D.,

METHODS

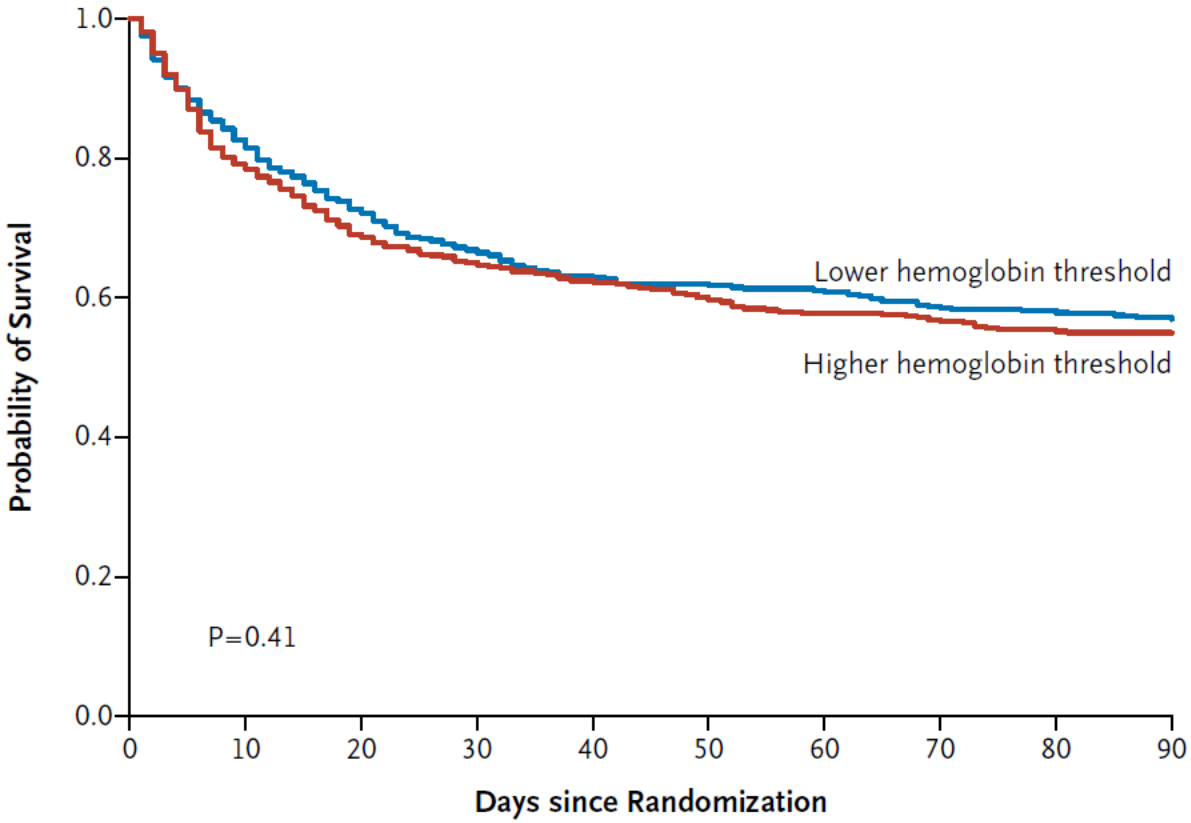
In this multicenter, parallel-group trial, we randomly assigned patients in the intensive care unit (ICU) who had septic shock and a hemoglobin concentration of 9 g per deciliter or less to receive 1 unit of leukoreduced red cells when the hemoglobin level was 7 g per deciliter or less (lower threshold) or when the level was 9 g per deciliter or less (higher threshold) during the ICU stay. The primary outcome measure was death by 90 days after randomization.

RESULTS

We analyzed data from 998 of 1005 patients (99.3%) who underwent randomization. The two intervention groups had similar baseline characteristics. In the ICU, the lower-threshold group received a median of 1 unit of blood (interquartile range, 0 to 3) and the higher-threshold group received a median of 4 units (interquartile range, 2 to 7). At 90 days after randomization, 216 of 502 patients (43.0%) assigned to the lower-threshold group, as compared with 223 of 496 (45.0%) assigned to the higher-threshold group, had died (relative risk, 0.94; 95% confidence interval, 0.78

This article was published on October 1, 2014, at NEJM.org.

A **Time to Death**



No. at Risk

Lower hemoglobin threshold	502	334	306	286
Higher hemoglobin threshold	496	321	287	273

Welchen Einfluss nimmt das Alter der EKs?

- multizentrische, verblindete randomisiert kontrollierte Studie
- 2430 Patienten, 64 Zentren

- „frische“ Blukonserven: 6,1 ± 4,9 Tage Lagerung
- Standardblutkonserven: 22,0 ± 8,4 Tage Lagerung

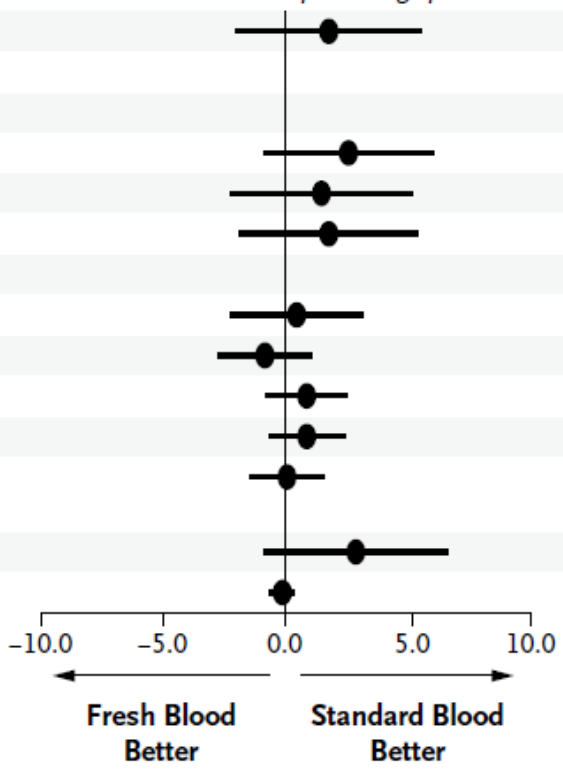
- primärer Outcome-Parameter: 90-Tage-Sterblichkeit

Lacroix J et al., The New England Journal of Medicine (2015)

Welchen Einfluss nimmt das Alter der EKs?

A Primary Outcome and Secondary Outcomes Related to Death and Major Illnesses

Outcome	Fresh Blood	Standard Blood	Absolute Risk Difference (95% CI)
	no. of patients/total no. (%)		*percentage points*
Primary outcome: death by day 90	448/1211 (37.0)	430/1219 (35.3)	1.7 (–2.1 to 5.5)
Secondary outcomes			
Death			
In ICU	324/1214 (26.7)	295/1217 (24.2)	2.5 (–1.0 to 5.9)
In hospital	403/1212 (33.3)	386/1211 (31.9)	1.4 (–2.3 to 5.1)
By day 28	371/1214 (30.6)	353/1225 (28.8)	1.7 (–1.9 to 5.4)
Major Illnesses			
Multiple organ dysfunction syndrome	162/1206 (13.4)	157/1207 (13.0)	0.4 (–2.3 to 3.1)
Acute respiratory distress syndrome	69/1206 (5.7)	80/1207 (6.6)	–0.9 (–2.8 to 1.0)
Cardiovascular failure	61/1206 (5.1)	51/1207 (4.2)	0.8 (–0.8 to 2.5)
Cardiac ischemia or infarction	54/1206 (4.5)	44/1207 (3.6)	0.8 (–0.7 to 2.4)
Deep-vein thrombosis or pulmonary embolism	43/1206 (3.6)	43/1207 (3.6)	0.0 (–1.5 to 1.5)
Nosocomial infection	411/1206 (34.1)	378/1207 (31.3)	2.8 (–0.9 to 6.5)
Acute transfusion reaction	4/1206 (0.3)	6/1207 (0.5)	–0.2 (–0.7 to 0.3)



Lacroix J et al., The New England Journal of Medicine (2015)

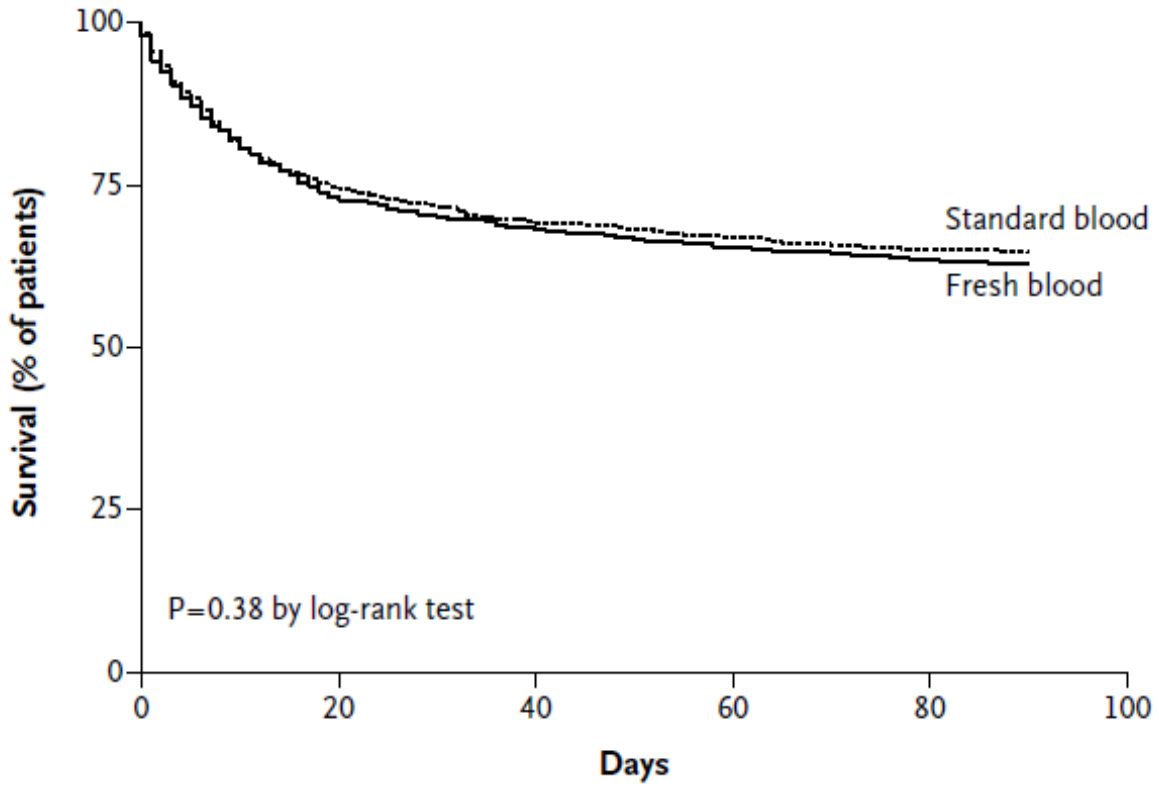


Figure 2. Kaplan–Meier Survival Analysis of Time to Death in the Intention-to-Treat Population.

The intention-to-treat population included 2430 patients. The hazard ratio in the fresh-blood group, as compared with the standard-blood group, was 1.1 (95% CI, 0.9 to 1.2).

Lacroix J et al., The New England Journal of Medicine (2015)

Keep them dry and
let them die?

vs

Gibt es ein „zu viel Flüssigkeit“ in der Sepsis?

New SSC recommendations

We recommend an initial fluid challenge in patients with sepsis-induced tissue hypoperfusion with suspicion of hypovolemia to achieve a minimum of 30mL/kg of crystalloids (a portion of this may be albumin equivalent). More rapid administration and greater amounts of fluid may be needed in some patients (grade 1C)

We recommend that a fluid challenge technique be applied wherein fluid administration is continued as long as there is hemodynamic improvement either based on dynamic (eg, change in pulse pressure, stroke volume variation) or static (eg, arterial pressure, heart rate) variables (UG)

RP Dellinger et al.
Crit Care Med 41, 580-637 (2013)

Critical Care Medicine
Society of Critical Care Medicine

New SSC recommendations

- We recommend norepinephrine as the first choice vasopressor (grade 1B)
- We suggest epinephrine (added to and potentially substituted for norepinephrine) when an additional agent is needed to maintain adequate blood pressure (grade 2B)
- Vasopressin (up to 0.03 U/min) can be added to norepinephrine with the intent of raising MAP to target or decreasing norepinephrine dosage (UG)
- We suggest dopamine as an alternative vasopressor agent to norepinephrine only in highly selected patients (eg, patients with low risk of tachyarrhythmias and absoulte or relative bradycardia (grade 2C)

RP Dellinger et al.
Crit Care Med 41, 580-637 (2013)
Critical Care Medicine
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New SSC recommendations

We recommend that a trial of dobutamine infusion up to 20µg/kg/min be administered or added to vasopressor (if in use) in the presence of (a) myocardial dysfunction, as suggested by elevated cardiac filling pressures and low cardiac output, or (b) ongoing signs of hypoperfusion, despite achieving adequate intravascular volume and adequate MAP (grade 1C)

RP Dellinger et al.
Crit Care Med 41, 580-637 (2013)

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Preliminary Communication | CARING FOR THE CRITICALLY ILL PATIENT

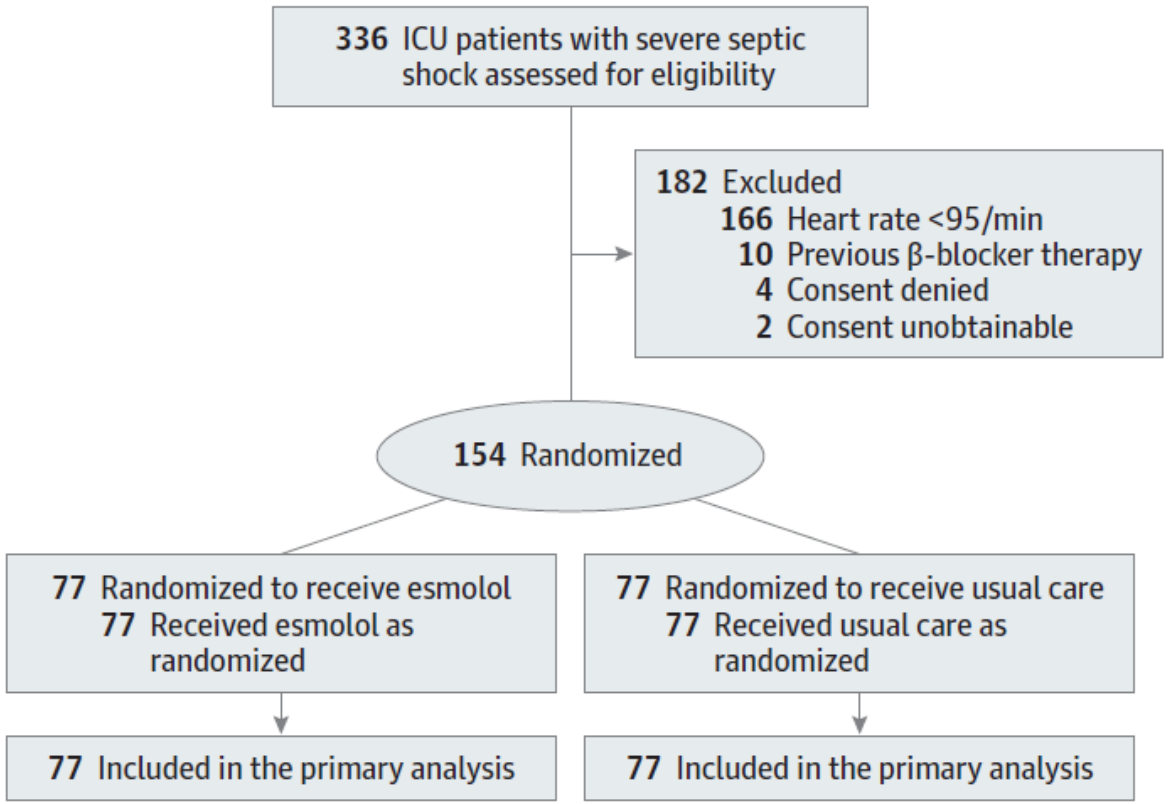
Effect of Heart Rate Control With Esmolol on Hemodynamic and Clinical Outcomes in Patients With Septic Shock

A Randomized Clinical Trial

JAMA. doi:10.1001/jama.2013.278477
Published online October 9, 2013.

Andrea Morelli, MD; Christian Ertmer, MD; Martin Westphal, MD; Sebastian Rehberg, MD; Tim Kampmeier, MD; Sandra Ligges, PhD; Alessandra Orecchioni, MD; Annalia D'Egidio, MD; Fiorella D'Ippoliti, MD; Cristina Raffone, MD; Mario Venditti, MD; Fabio Guarracino, MD; Massimo Girardis, MD; Luigi Tritapepe, MD; Paolo Pietropaoli, MD; Alexander Mebazaa, MD; Mervyn Singer, MD, FRCP

Figure 1. Flow Chart



Preliminary Communication | CARING FOR THE CRITICALLY ILL PATIENT

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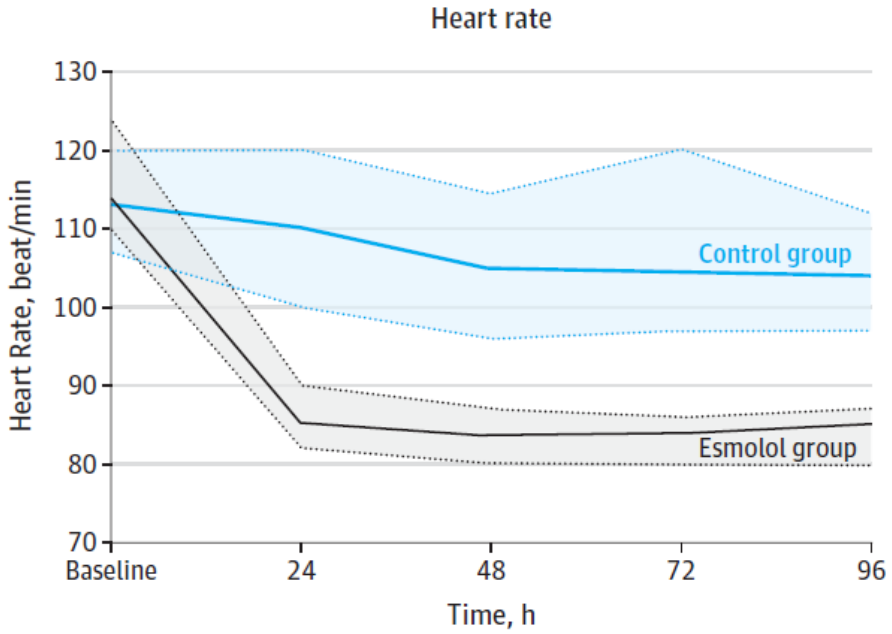
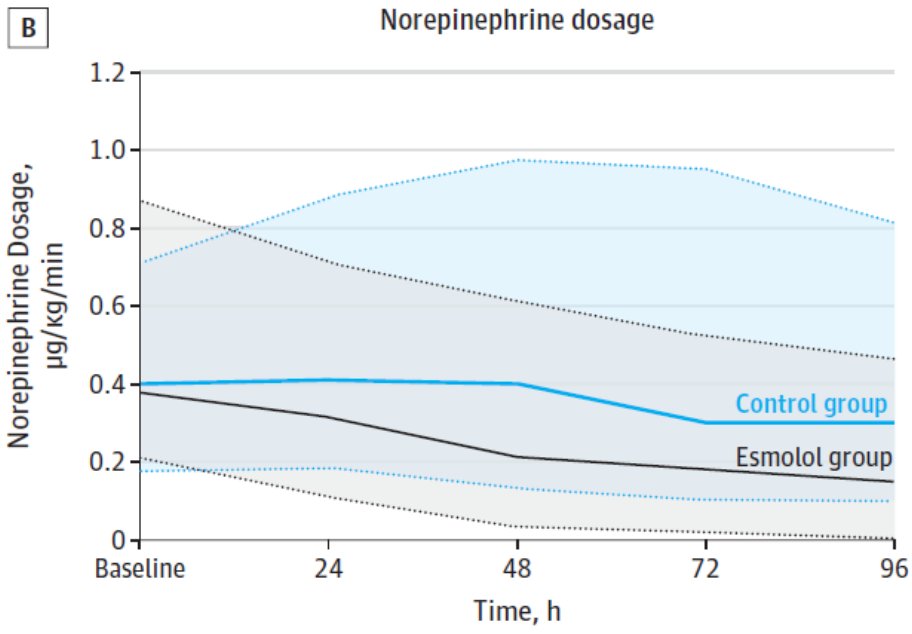




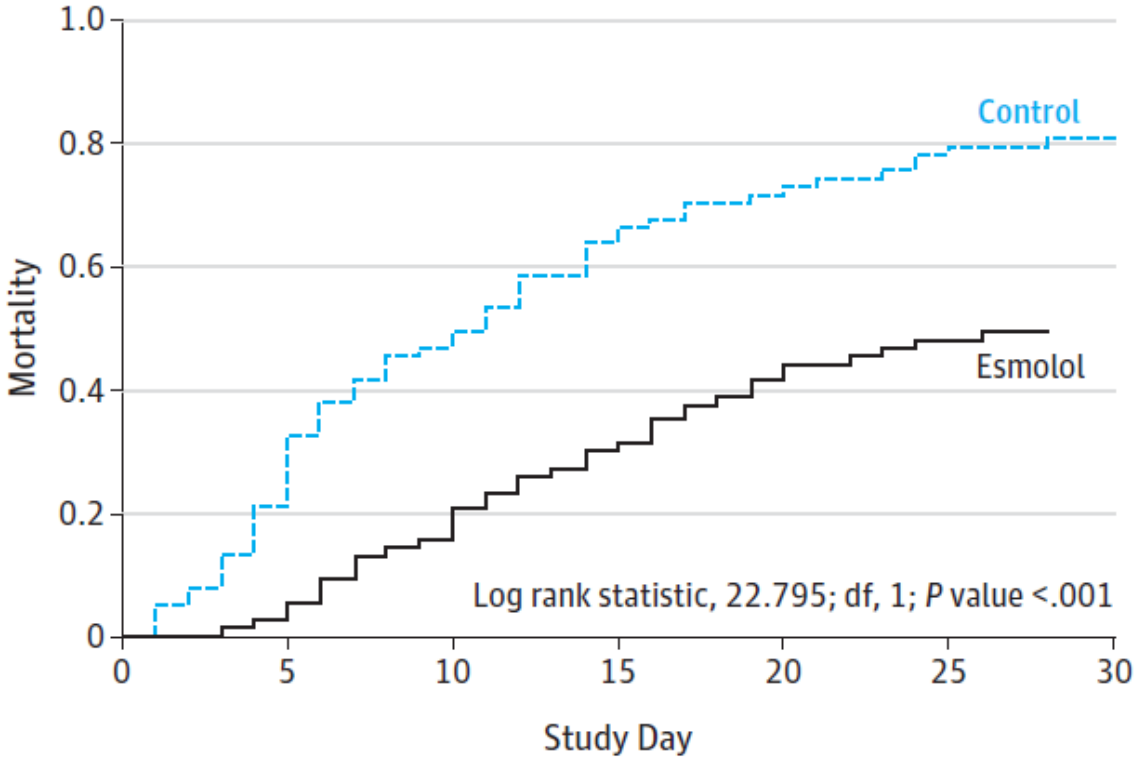
Preliminary Communication | CARING FOR THE CRITICALLY ILL PATIENT

Effect of Heart Rate Control With Esmolol on Hemodynamic and Clinical Outcomes in Patients With Septic Shock

A Randomized Clinical Trial

JAMA. doi:10.1001/jama.2013.278477
Published online October 9, 2013.

A Univariate survival analysis



No. at risk							
Control	77	52	39	26	21	16	15
Esmolol	77	73	61	53	43	40	39

New SSC recommendations

- Target a tidal volume of 6mL/kg predicted body weight in patients with sepsis-induced ARDS (grade 1A vs. 12 mL/kg)

- A short course of NMBA of not greater than 48 hours with early sepsis-induced ARDS and a PaO2/FiO2 < 150 mmHg (grade 2C)

- Recruitment maneuvers be used in sepsis patients with severe refractory hypoxemia (grade 2C)

- We suggest prone positioning in sepsis-induced ARDS patients with a PaO2/FiO2 ratio ≤ 100 mmHg in facilities that have experience with such practices (grade 2B)

RP Dellinger et al.
Crit Care Med 41, 580-637 (2013)

Critical Care Medicine
Society of Critical Care Medicine

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JUNE 6, 2013 VOL. 368 NO. 23

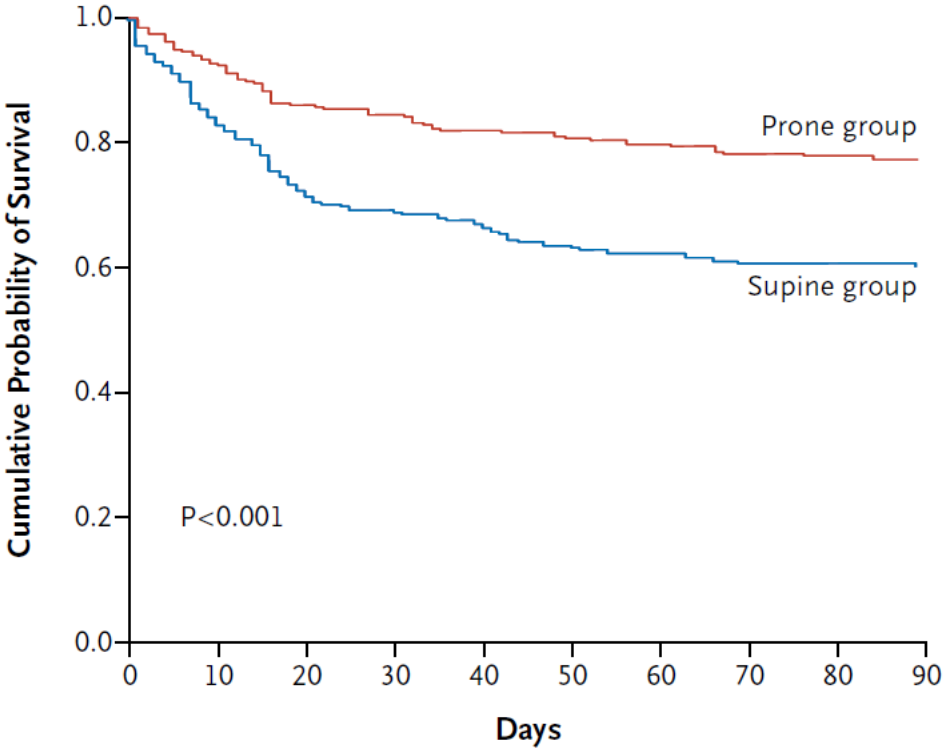
Prone Positioning in Severe Acute Respiratory Distress Syndrome

Claude Guérin, M.D., Ph.D., Jean Reignier, M.D., Ph.D., Jean-Christophe Richard, M.D., Ph.D., Pascal Beuret, M.D., Arnaud Gacouin, M.D., Thierry Boulain, M.D., Emmanuelle Mercier, M.D., Michel Badet, M.D., Alain Mercat, M.D., Ph.D., Olivier Baudin, M.D., Marc Clavel, M.D., Delphine Chatellier, M.D., Samir Jaber, M.D., Ph.D., Sylvène Rosselli, M.D., Jordi Mancebo, M.D., Ph.D., Michel Sirodot, M.D., Gilles Hilbert, M.D., Ph.D., Christian Bengler, M.D., Jack Richecoeur, M.D., Marc Gainnier, M.D., Ph.D., Frédérique Bayle, M.D., Gael Bourdin, M.D., Véronique Leray, M.D., Raphaele Girard, M.D., Loredana Baboi, Ph.D., and Louis Ayzac, M.D., for the PROSEVA Study Group*

In this multicenter, prospective, randomized, controlled trial, we randomly assigned 466 patients with severe ARDS to undergo prone-positioning sessions of at least 16 hours or to be left in the supine position. Severe ARDS was defined as a ratio of the partial pressure of arterial oxygen to the fraction of inspired oxygen (FIO_2) of less than 150 mm Hg, with an FIO_2 of at least 0.6, a positive end-expiratory pressure of at least 5 cm of water, and a tidal volume close to 6 ml per kilogram of predicted body weight. The primary outcome was the proportion of patients who died from any cause within 28 days after inclusion.

per kilogram of predicted body weight; the criteria were confirmed after 12 to 24 hours of mechanical ventilation in the participating intensive

Patienten mit Sepsis>80%



No. at Risk

Prone group	237	202	191	186	182
Supine group	229	163	150	139	136

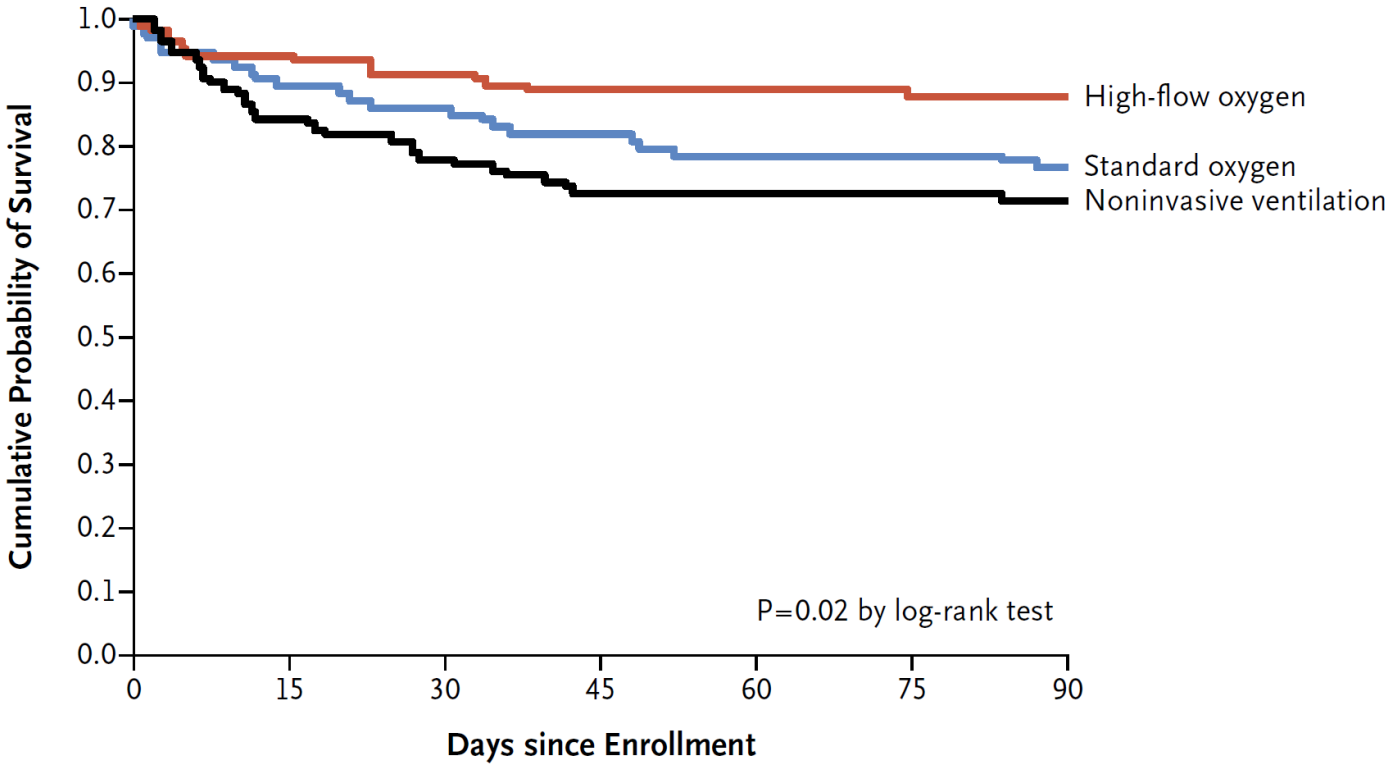
Figure 2. Kaplan–Meier Plot of the Probability of Survival from Randomization to Day 90.

ORIGINAL ARTICLE

High-Flow Oxygen through Nasal Cannula in Acute Hypoxemic Respiratory Failure

Jean-Pierre Frat, M.D., Arnaud W. Thille, M.D., Ph.D., Alain Mercat, M.D., Ph.D.,

This article was published on May 17, 2015, at NEJM.org.



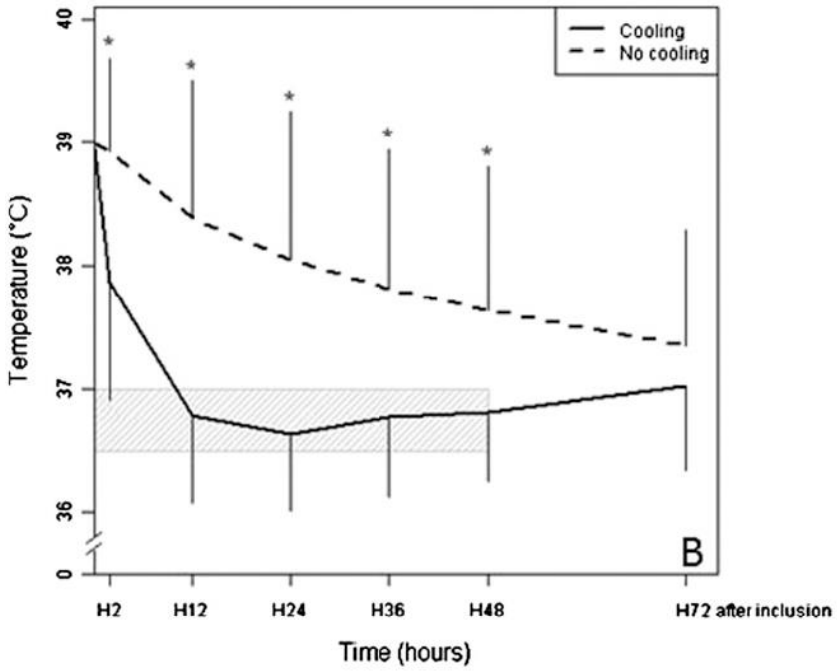
Fever Control Using External Cooling in Septic Shock

A Randomized Controlled Trial

Frédérique Schortgen[1,2], Karine Clabault[3], Sandrine Katsahian[4], Jerome Devaquet[5], Alain Mercat[6], Nicolas Deye[7], Jean Dellamonica[8], Lila Bouadma[9], Fabrice Cook[10], Olfa Beji[1], Christian Brun-Buisson[1], François Lemaire[1], and Laurent Brochard[1,2,11]

Am J Respir Crit Care Med Vol 185, Iss. 10, pp 1088–1095, May 15, 2012

Methods: In a multicenter randomized controlled trial, febrile patients with septic shock requiring vasopressors, mechanical ventilation, and sedation were allocated to external cooling (n = 101) to achieve normothermia (36.5–37°C) for 48 hours or no external cooling (n = 99). Vasopressors were tapered to maintain the same blood pressure target in the two groups. The primary endpoint was the number of patients with a 50% decrease in baseline vasopressor dose after 48 hours.



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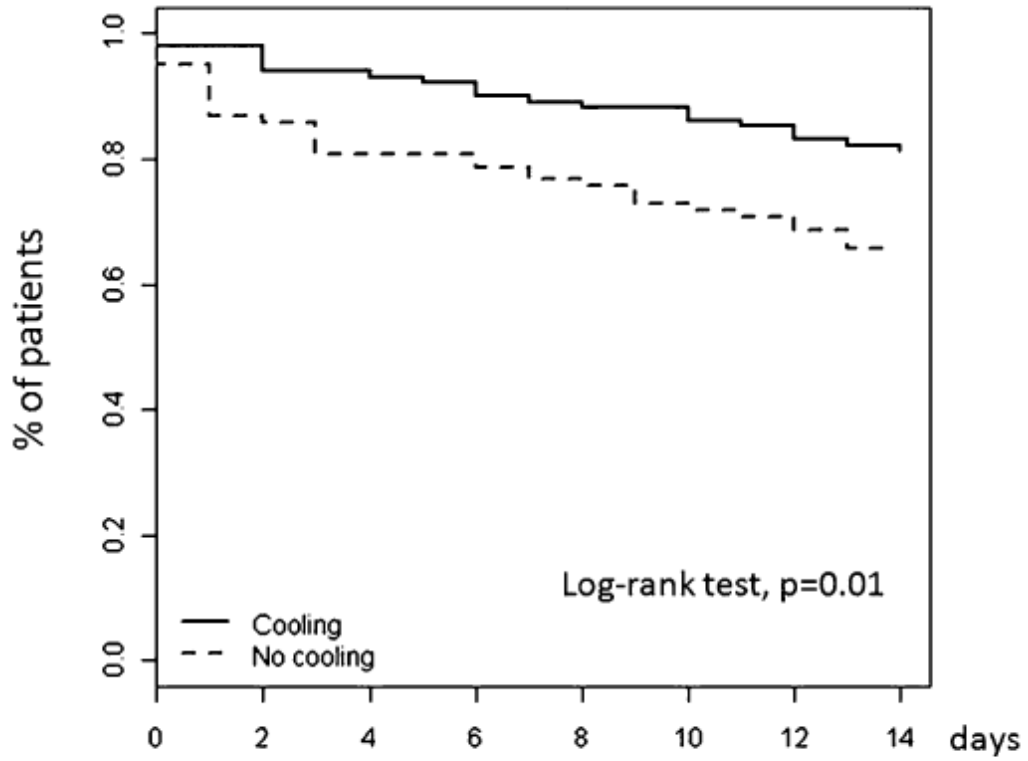


Figure 5. Kaplan-Meier survival curve for mortality until Day 14.

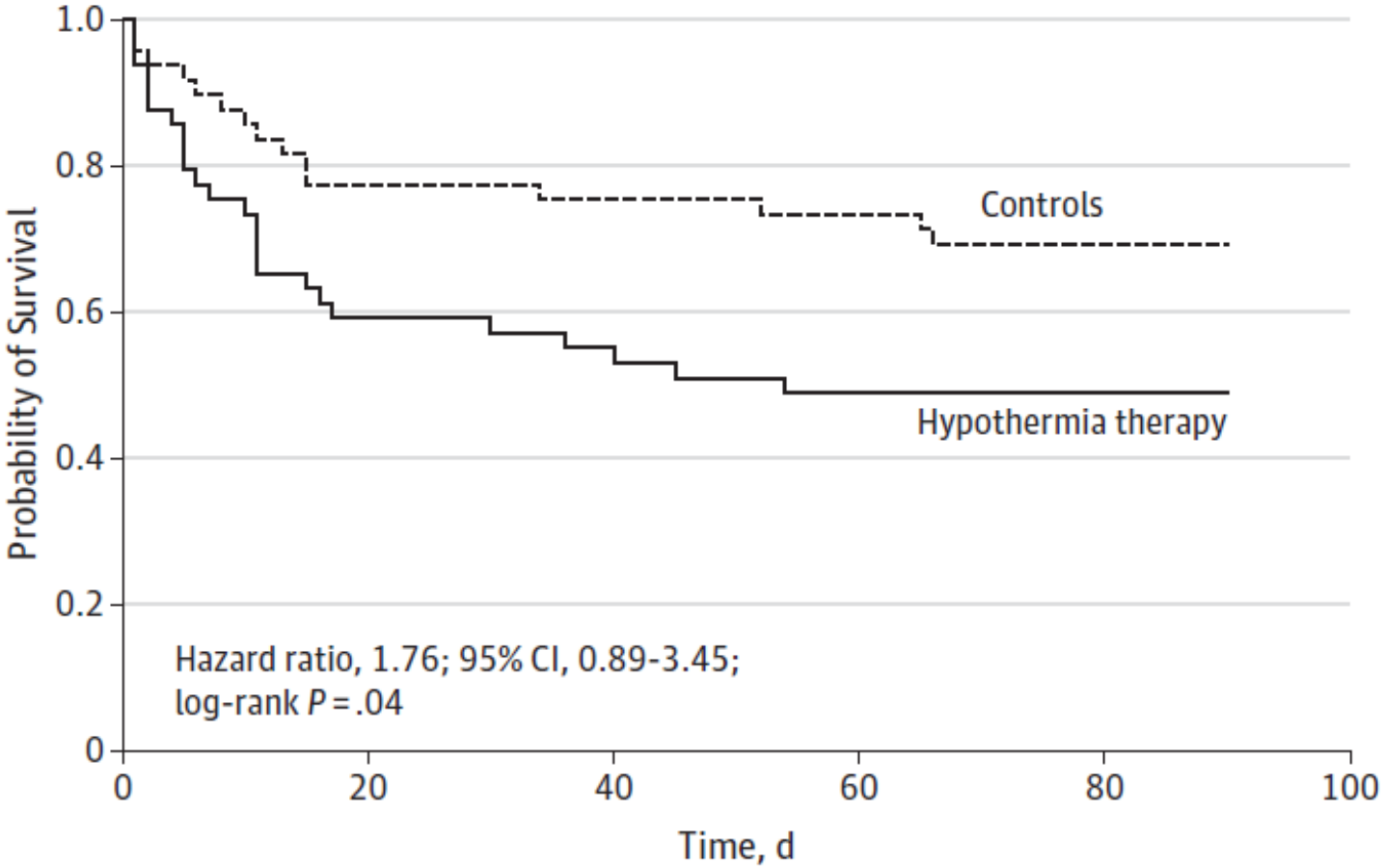
Original Investigation | CARING FOR THE CRITICALLY ILL PATIENT

Induced Hypothermia in Severe Bacterial Meningitis

A Randomized Clinical Trial

JAMA. doi:10.1001/jama.2013.280506
Published online October 8, 2013.

Bruno Mourvillier, MD; Florence Tubach, MD, PhD; Diederik van de Beek, MD, PhD; Denis Garot, MD; Nicolas Pichon, MD; Hugues Georges, MD;



Klinisches Management des Patienten mit Sepsis

~~Aktiviertes Protein C~~

Metabolische Kontrolle?

Hydrokortison?

Immunglobuline?

Selen?

New SSC recommendations

- We recommend a protocolized approach to blood glucose management in ICU patients with severe sepsis, commencing insulin dosing when two consecutive blood glucose levels are > 180 mg/dL. This approach should target an upper blood glucose level ≤ 180mg/dL rather than an upper target blood glucose ≤ 110 mg/dL (grade 1A)

Und die untere Grenze?
Möglichst geringe Schwankungen

RP Dellinger et al.
Crit Care Med 41, 580-637 (2013)

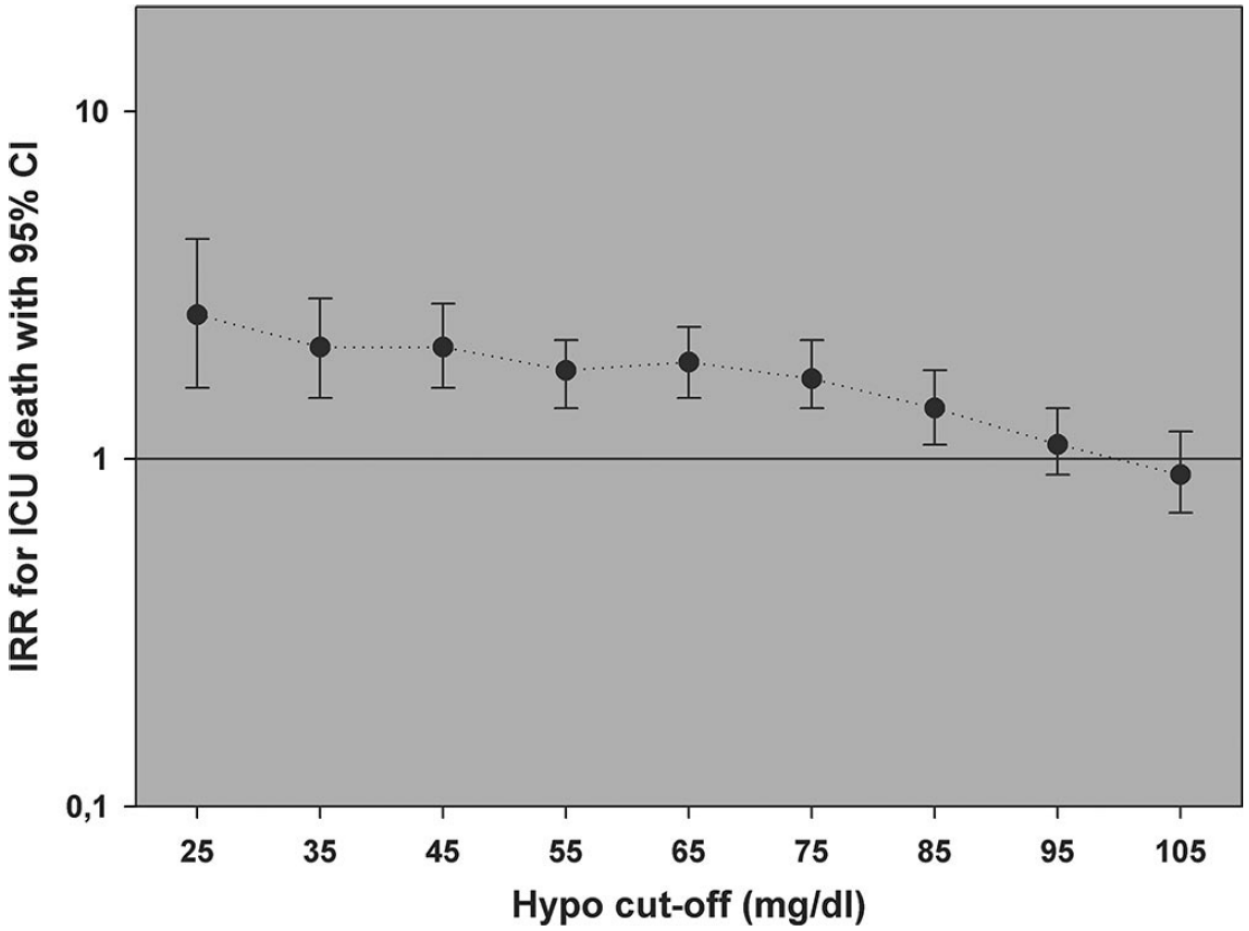
Critical Care Medicine
Society of Critical Care Medicine

Hypoglycemia is associated with intensive care unit mortality*

Jeroen Hermanides, MD; Robert J. Bosman, MD, PhD; Titia M. Vriesendorp, MD, PhD; Ron Dotsch, MSc; Frits R. Rosendaal, MD, PhD; Durk F. Zandstra, MD, PhD; Joost B. L. Hoekstra, MD, PhD; J. Hans DeVries, MD, PhD

Crit Care Med 2010 Vol. 38, No. 6

Welcher cut off?



Welche Rolle spielen

Kaliumverschiebungen

Lipolysehemmung

im Rahmen der intensivierten Insulintherapie

New SSC recommendations

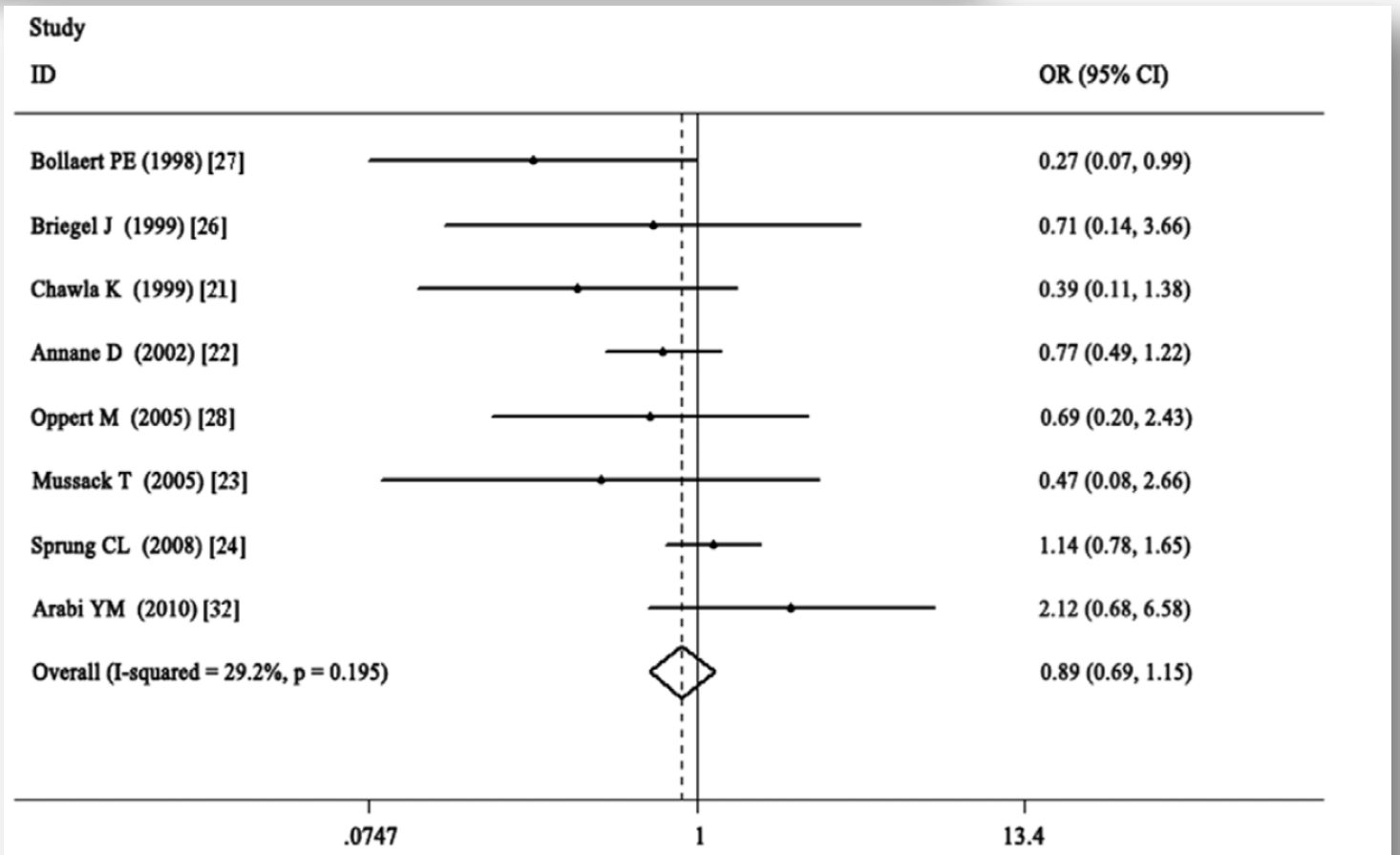
- We suggest not using intravenous hydrocortisone as a treatment of adult septic shock patients if adequate fluid resuscitation and vasopressor therapy are able to restore hemodynamic stability. If this is not achievable, we suggest intravenous hydrocortisone alone at a dose of 200 mg per day (grade 2C)

RP Dellinger et al.
Crit Care Med 41, 580-637 (2013)
Critical Care Medicine

Low-Dose Hydrocortisone Therapy Attenuates Septic Shock in Adult Patients but Does Not Reduce 28-Day Mortality: A Meta-Analysis of Randomized Controlled Trials

(Anesth Analg 2014;118:346–57)

Changsong Wang, MD,* Jiaxiao Sun, MSc,* Juanjuan Zheng, MSc,† Lei Guo, MD,* Hongyan Ma, MD,* Yang Zhang,* Fengmin Zhang, PhD,†§ and Enyou Li, MD*



of low-dose hydrocortisone therapy on mortality at 28 days in patients with septic shock.

Vergleich Annane und Corticus

	Annane	CORTICUS
Mortality Rate Placebo	63%	31%
Time range for inclusion	8 h	72 h
Add. Fludrocortisone	Yes	No
Tapering Off HC	No	Yes
Treatment time	7 d	11 d
Surgical patients	40%	67%
RR_{sys} < 90 mmHg	> 1 h	< 1 h

Dia H. Gerlach

Corticosteroids and pneumonia: time to change practice

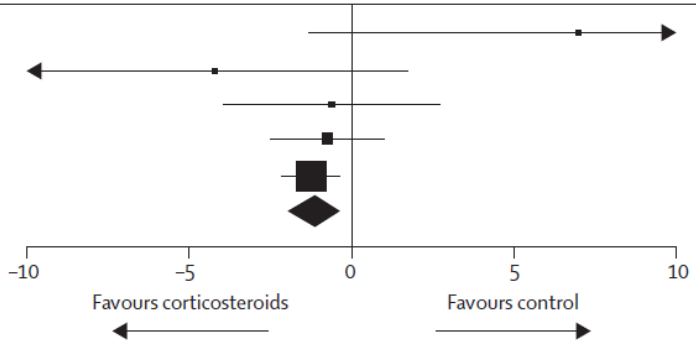
Published Online
January 19, 2015
http://dx.doi.org/10.1016/
S0140-6736(14)62391-6

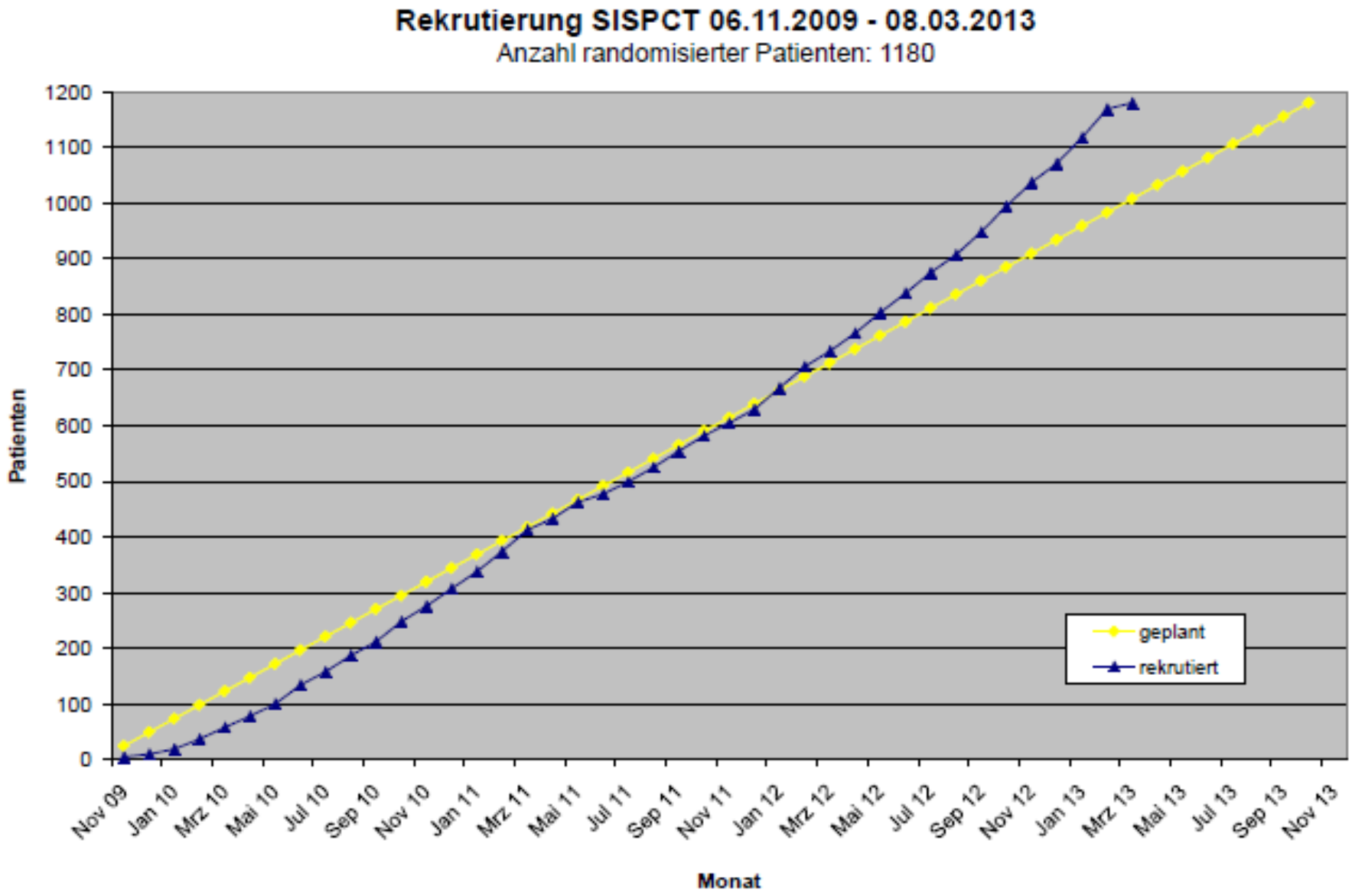
See Online/Articles
http://dx.doi.org/10.1016/
S0140-6736(14)62447-8

Djillali Annane
Raymond Poincaré Hospital AP-HP, University of Versailles SQY, and Laboratory Cell Death, Inflammation and Infection U1173 (INSERM), 92380 Garches, France
djillali.annane@rpc.aphp.fr

	Experimental		Control		Mean difference	
	Mean (SD)	Total	Mean (SD)	Total	Weight	IV, fixed (95% CI)
Confalonieri (2005)[7]	29·25 (17·25)	23	22·25 (10·75)	23	0·8%	7·00 (−1·31 to 15·31)
Mikami (2007)[8]	11·3 (5·5)	15	15·5 (10·7)	16	1·7%	−4·20 (−10·14 to 1·74)
Snijders (2010)[11]	10 (12)	104	10·6 (12·8)	109	5·3%	−0·60 (−3·93 to 2·73)
Meijvis (2011)[9]	8·84 (8·13)	151	9·58 (7·57)	153	18·7%	−0·74 (−2·51 to 1·03)
Blum (2015)[5]	7·63 (5·9)	392	8·88 (6·8)	393	73·5%	−1·25 (−2·14 to −0·36)
Total (95% CI)		**685**		**694**	**100·0%**	**−1·10 (−1·86 to −0·34)**

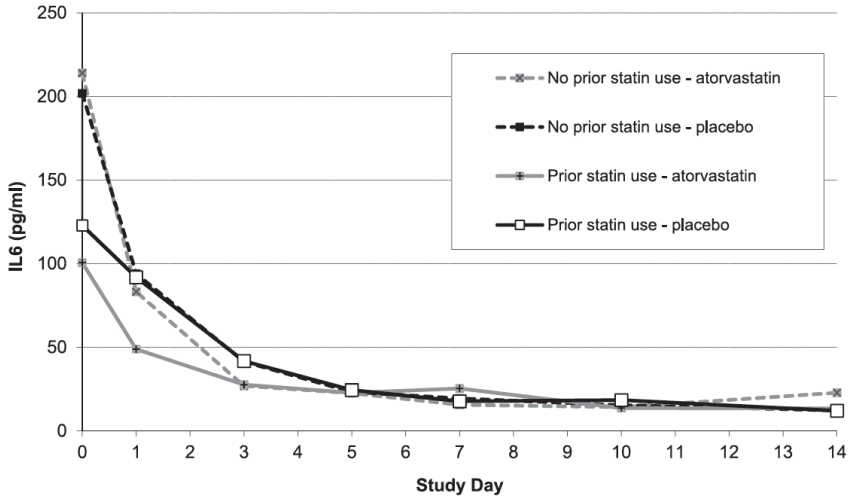
Heterogeneity χ^2=5·06, df=4 (p=0·28) I^2=21%
Test for overall effect Z=2·82 (p=0·005)




Rekrutierung SISPCT 06.11.2009 - 08.03.2013
Anzahl randomisierter Patienten: 1180
Patienten
1200
1100
1000
900
800
700
600
500
400
300
200
100
0
Nov 09
Jan 10
Mrz 10
Mai 10
Jul 10
Sep 10
Nov 10
Jan 11
Mrz 11
Mai 11
Jul 11
Sep 11
Nov 11
Jan 12
Mrz 12
Mai 12
Jul 12
Sep 12
Nov 12
Jan 13
Mrz 13
Mai 13
Jul 13
Sep 13
Nov 13
Monat
geplant
rekrutiert

Was bisher geschah… Statine

Plasma IL-6



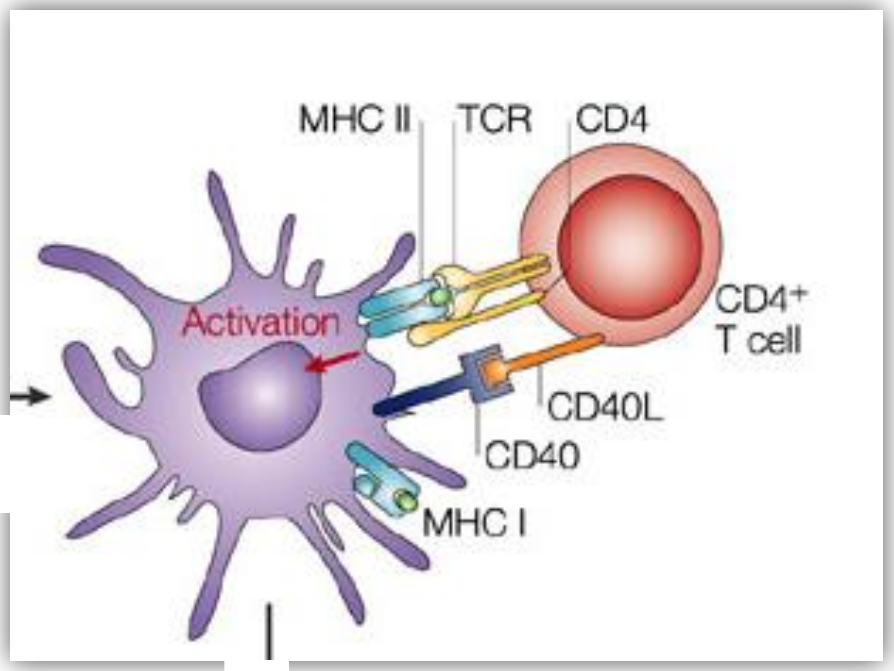
	Entire Cohort			*De Novo* = No Prior Statin Use			Prior Statin Use		
Characteristic	Atorvastatin (*n* = 123)	Placebo (*n* = 127)	*P* Value	Atorvastatin (*n* = 86)	Placebo (*n* = 87)	*P* Value	Atorvastatin (*n* = 37)	Placebo (*n* = 40)	*P* Value
ICU mortality, % (n)	7% (9)	12% (15)	0.23	7% (6)	8% (7)	0.79	8% (3)	20% (8)	0.14
Hospital mortality, % (n)	13% (16)	18% (23)	0.27	14% (12)	13.8% (12)	0.98	11% (4)	28% (11)	0.06
28-d mortality, % (n)	10% (12)	17% (22)	0.09	11.6% (10)	12.6% (11)	0.86	5% (2)	28% (11)	0.01
90-d mortality, % (n)	15% (18)	19% (24)	0.38	16.3% (14)	14.9% (13)	0.78	11% (4)	28% (11)	0.06
ICU LOS, d, median (IQR)	5.6 (3.1–9.7)	6.6 (2.9–13.2)	0.28	5.7 (3.1–9.0)	8.5 (3.0–14.1)	0.03	5.0 (3.1–9.9)	3.9 (2.5–10.5)	0.23
Hospital LOS, d, median (IQR)	18.3 (11.0–38.7)	22.7 (12.4–37.0)	0.48	17.84 (9.9–38.7)	23.0 (12.6–37.9)	0.37	20.8 (11.6–38.9)	20.6 (12.3–34.3)	0.91
	Odds Ratio: Atorvastatin versus Placebo								
Age-adjusted 28-d mortality	0.56 (0.26–1.20)		0.14	0.97 (0.38–2.43)		0.94	0.17 (0.03–0.85)		0.03
Age-adjusted 90-d mortality	0.84 (0.42–1.66)		0.60	1.26 (0.54–2.92)		0.59	0.33 (0.09–1.22)		0.10
Age-adjusted hospital mortality	0.73 (0.36–1.49)		0.39	1.26 (0.54–2.92)		0.59	0.33 (0.09–1.22)		0.10

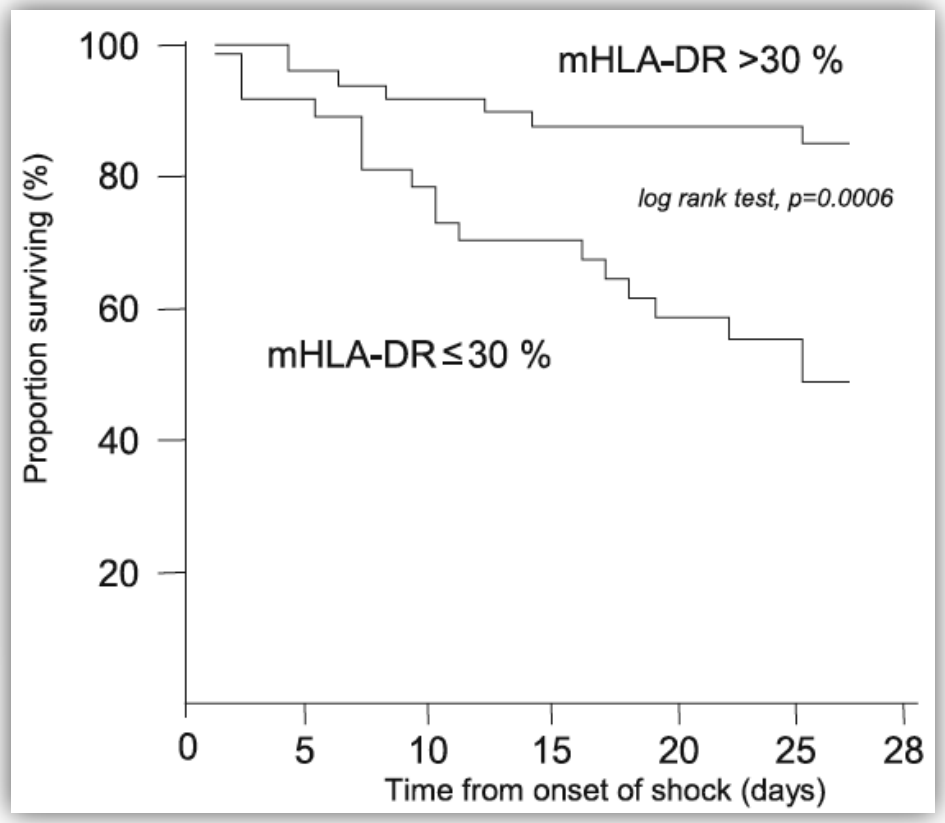
Kruger P, *Am J Respir Crit Care Med* (2013)

Statine unbedingt
weitergeben
aber
nicht neu ansetzen

Regeneration des Immunsystems?

Monocytic HLA-DR – a hallmark of immunosuppression



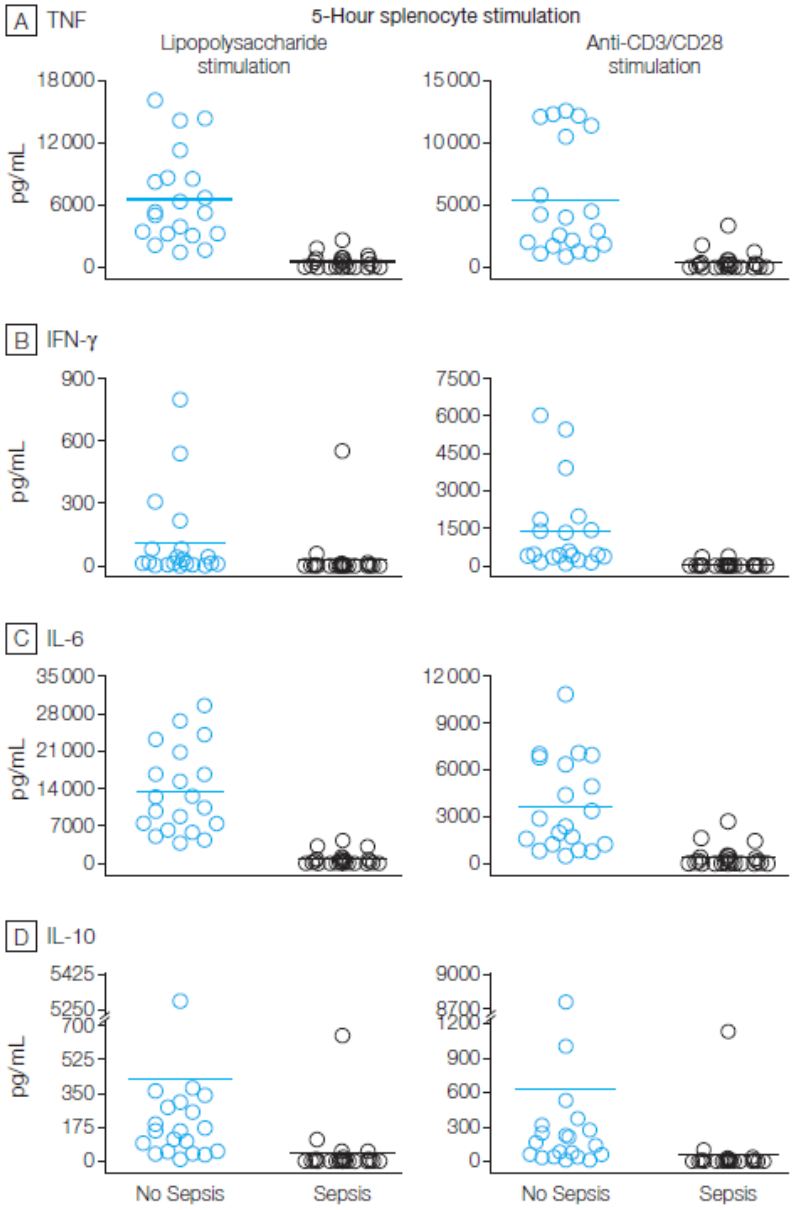


Monneret et al., *Intensive. Care. Med. (*2006)

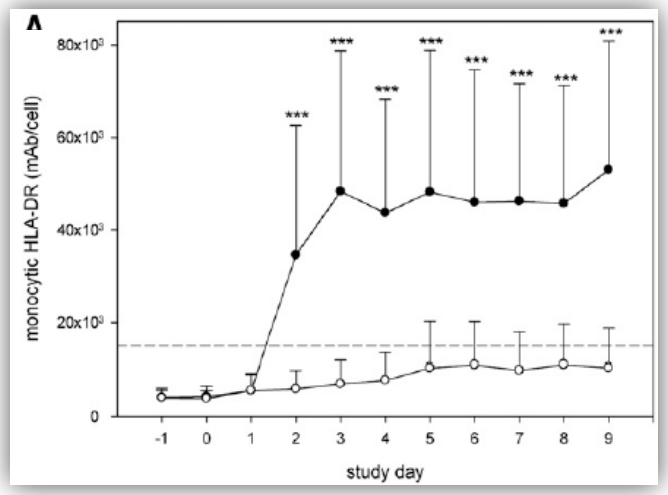
Immunosuppression in Patients Who Die of Sepsis and Multiple Organ Failure

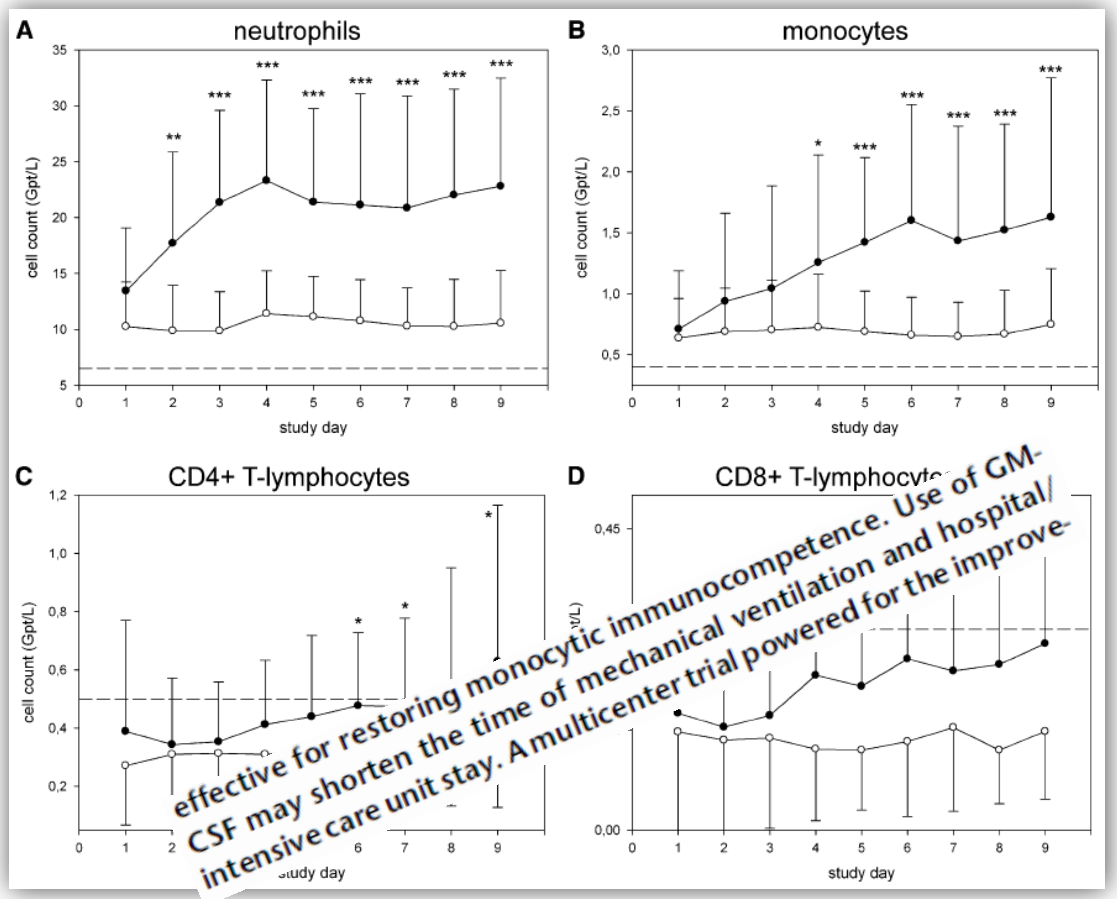
Jonathan S. Boomer, PhD
Kathleen To, MD
Kathy C. Chang, PhD
Osamu Takasu, MD
Dale F. Osborne, BS
Andrew H. Walton, MS
Traci L. Bricker, BS
Stephen D. Jarman II, BSN, RN
Daniel Kreisel, MD, PhD
Alexander S. Krupnick, MD
Anil Srivastava, MD
Paul E. Swanson, MD
Jonathan M. Green, MD
Richard S. Hotchkiss, MD

JAMA. 2011;306(23):2594-2605



GM-CSF reverses sepsis associated immunosuppression



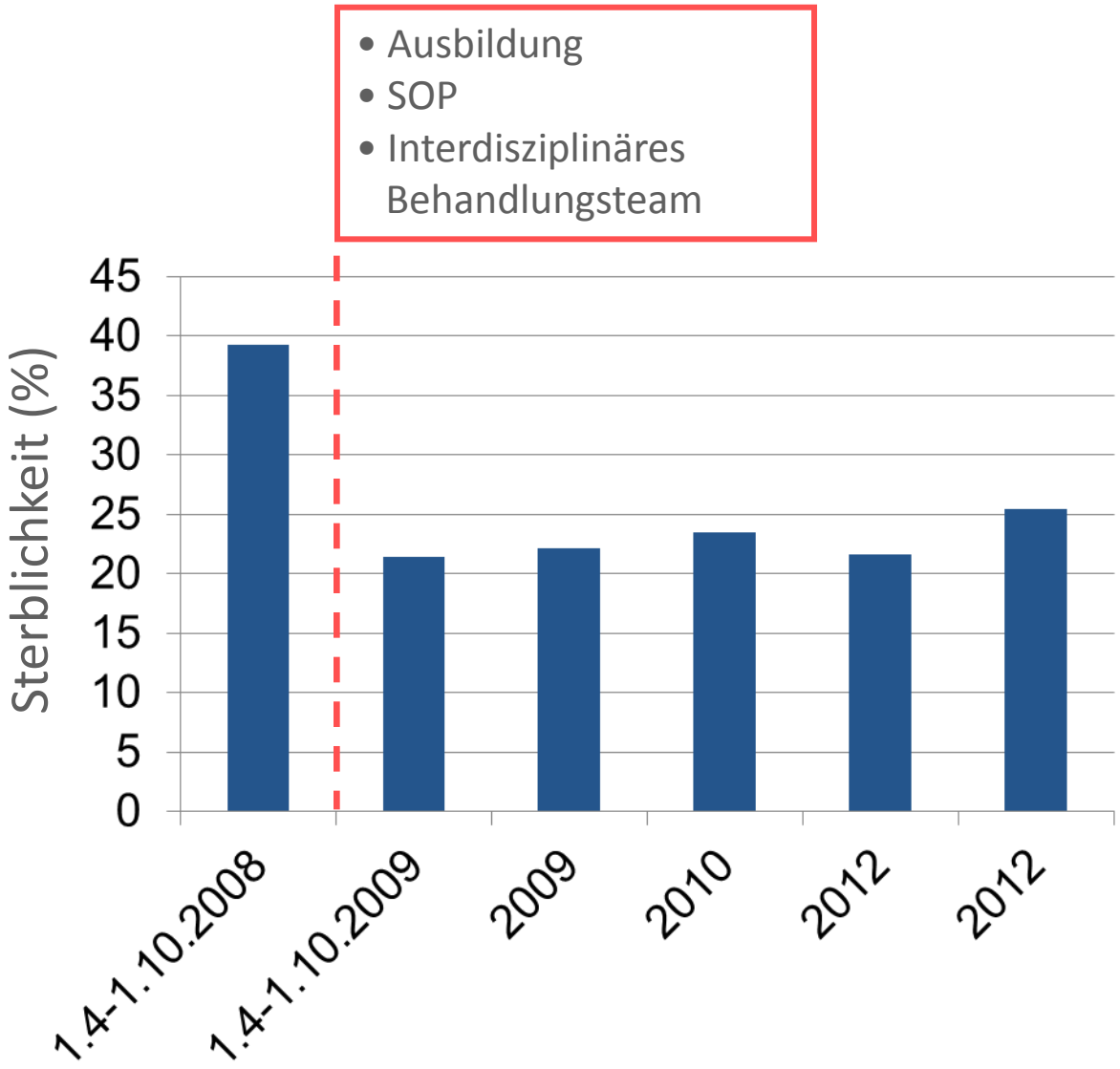


→ „... the first controlled biomarker-guided immunostimulatory trial in sepsis."
(Meisel et al., *Am J Respir Crit Care Med* (2008))

Interdisziplinäre Therapie

Intensivsterblichkeit

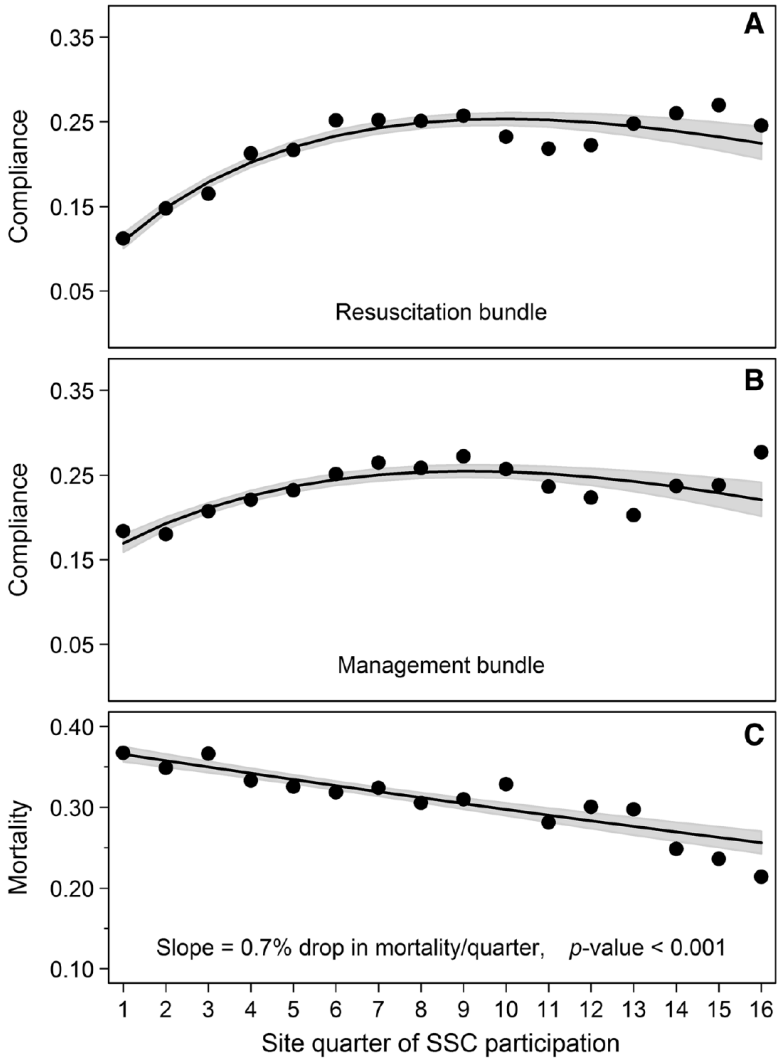
Patienten >24h Beatmet (DKR) / LOS > 24h



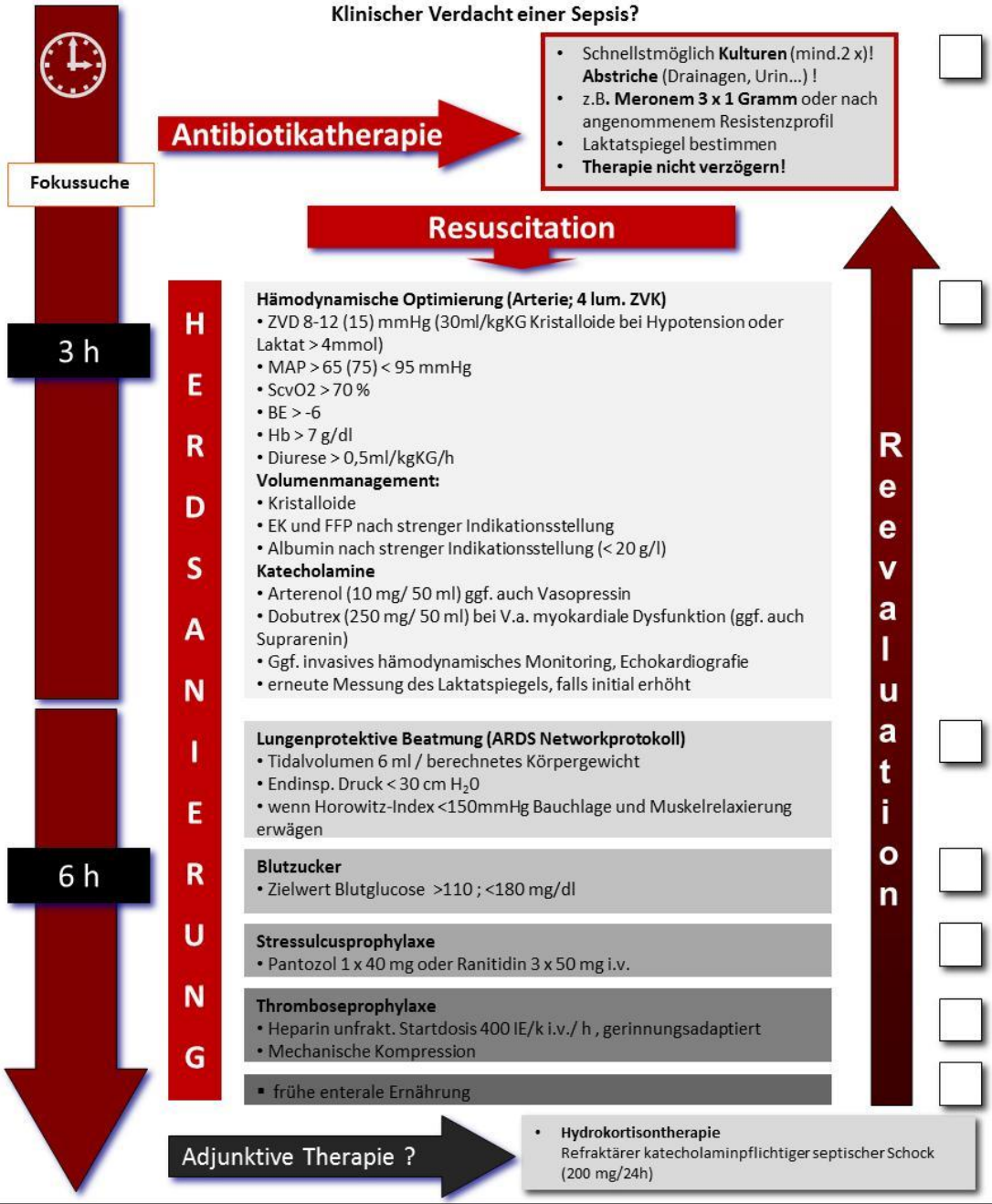
Mitchell M. Levy
Andrew Rhodes
Gary S. Phillips
Sean R. Townsend
Christa A. Schorr
Richard Beale
Tiffany Osborn
Stanley Lemeshow
Jean-Daniel Chiche
Antonio Artigas
R. Phillip Dellinger

Surviving Sepsis Campaign: association between performance metrics and outcomes in a 7.5-year study

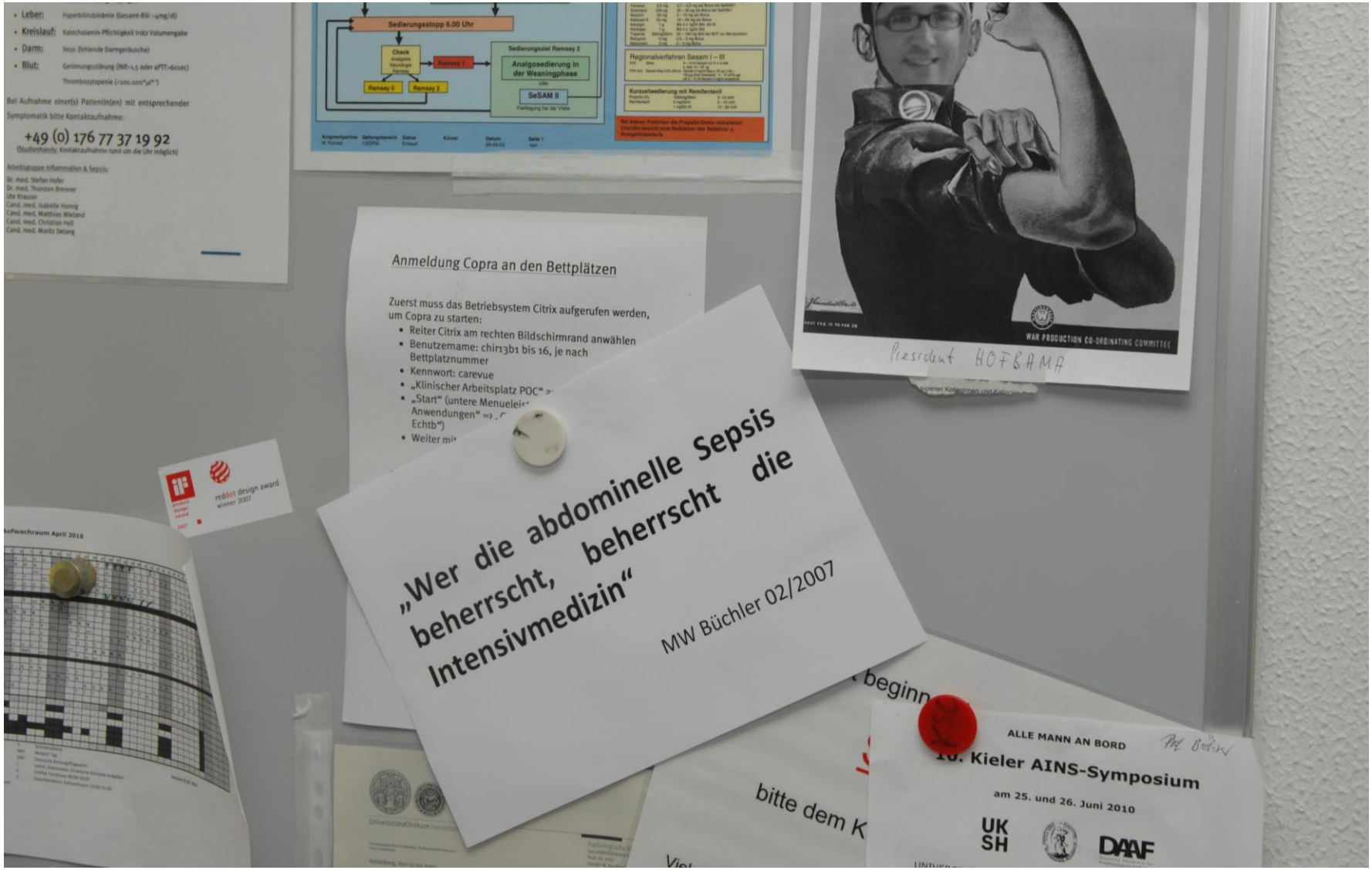
Intensive Care Med (2014) 40:1623–1633



Heidelberger Sepsis-Pathway



Ansprechpartner	Geltungsbereich	Status	Überprüft	Freigegeben	Kürzel	Datum	Seite 1
Prof. M. Weigand	Station 13 / AWR	gültig		Weigand	SepPathHD	23-1--2015	


Leber:
Kreislauf:
Darm:
Blut:
+49 (0) 176 77 37 19 92
Sedierungsstopp 6.00 Uhr
Sedierungsziel Ramsay 2
Analgosedierung in der Weaningphase
SeSAM II
Regionalverfahren Sesam I – III
Kurzzeitsedierung mit Remifentanil
Anmeldung Copra an den Bettplätzen
Zuerst muss das Betriebsystem Citrix aufgerufen werden, um Copra zu starten:
Reiter Citrix am rechten Bildschirmrand anwählen
Benutzername: chir13b1 bis 16, je nach Bettplatznummer
Kennwort: carevue
„Klinischer Arbeitsplatz POC"
„Start" (untere Menueleiste „Anwendungen" => „Echtb")
Weiter mit
„Wer die abdominelle Sepsis beherrscht, beherrscht die Intensivmedizin"
MW Büchler 02/2007
WAR PRODUCTION CO-ORDINATING COMMITTEE
President HOFBAMA
reddot design award winner 2007
Aufwachraum April 2010
ALLE MANN AN BORD
10. Kieler AINS-Symposium
am 25. und 26. Juni 2010
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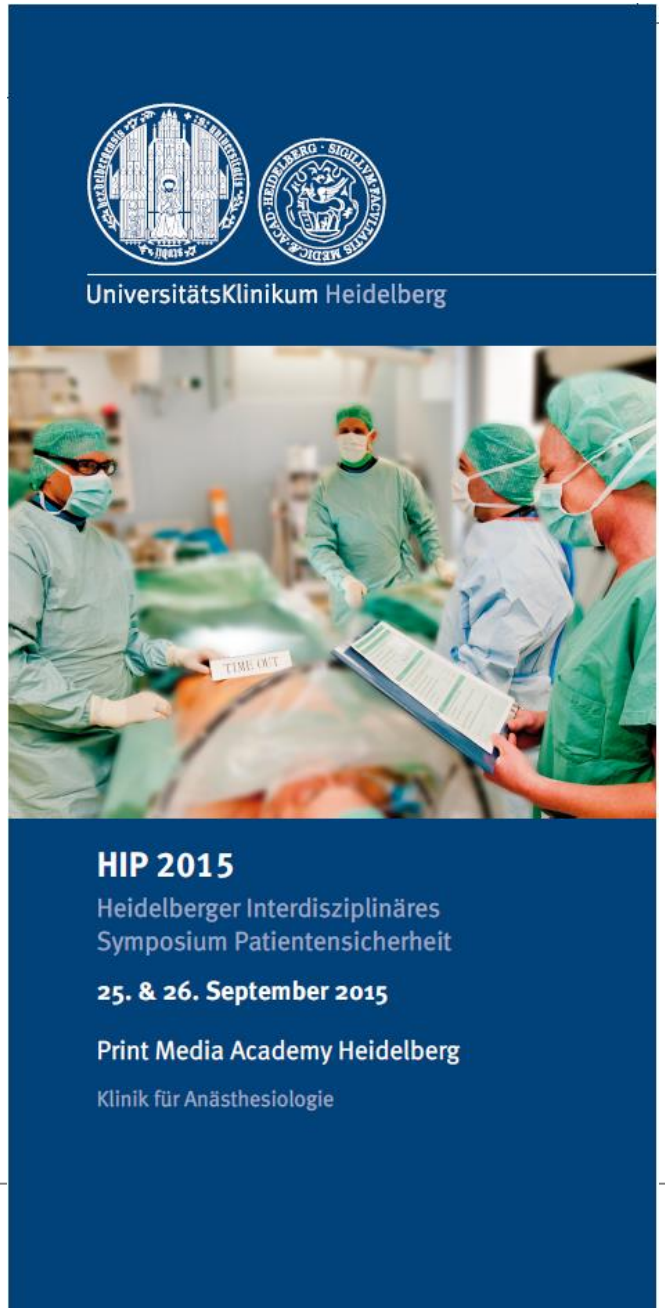

Danke für Ihre Aufmerksamkeit!

markus.weigand@med.uni-heidelberg.de

Danke für Ihre Aufmerksamkeit!

markus.weigand@med.uni-heidelberg.de

“detoxification“

Effects of Fluid Resuscitation With Colloids vs Crystalloids on Mortality in Critically Ill Patients Presenting With Hypovolemic Shock

The CRISTAL Randomized Trial

JAMA. doi:10.1001/jama.2013.280502
Published online October 9, 2013.

Djillali Annane, MD, PhD; Shidasp Siami, MD; Samir Jaber, MD, PhD; Claude Martin, MD, PhD; Souheil Elatrous, MD; Adrien Descorps Declère, MD; Jean Charles Preiser, MD; Hervé Outin, MD; Gilles Troché, MD; Claire Charpentier, MD; Jean Louis Trouillet, MD; Antoine Kimmoun, MD; Xavier Forceville, MD, PhD; Michael Darmon, MD; Olivier Lesur, MD, PhD; Jean Régnier, MD; Fékri Abroug, MD; Philippe Berger, MD; Christophe Clech, MD; Joël Cousson, MD; Laure Thibault, MD; Sylvie Chevret, MD, PhD; for the CRISTAL Investigators

To be eligible, research participants had to have received no prior fluids for resuscitation during their ICU stay and now require fluid resuscitation for acute hypovolemia as defined by the combination of (1) hypotension: systolic arterial pressure of less than 90 mm Hg, mean arterial pressure of less than 60 mm Hg, orthostatic hypotension (ie, a decrease in systolic arterial pressure of at least 20 mm Hg from the supine to the semirecumbent position), or a delta pulse pressure of 13% or higher; (2) evidence for low filling pressures and low cardiac index as assessed either invasively or noninvasively; and (3) signs of tissue hypoperfusion or hypoxia, including at least 2 of the following clinical symp-

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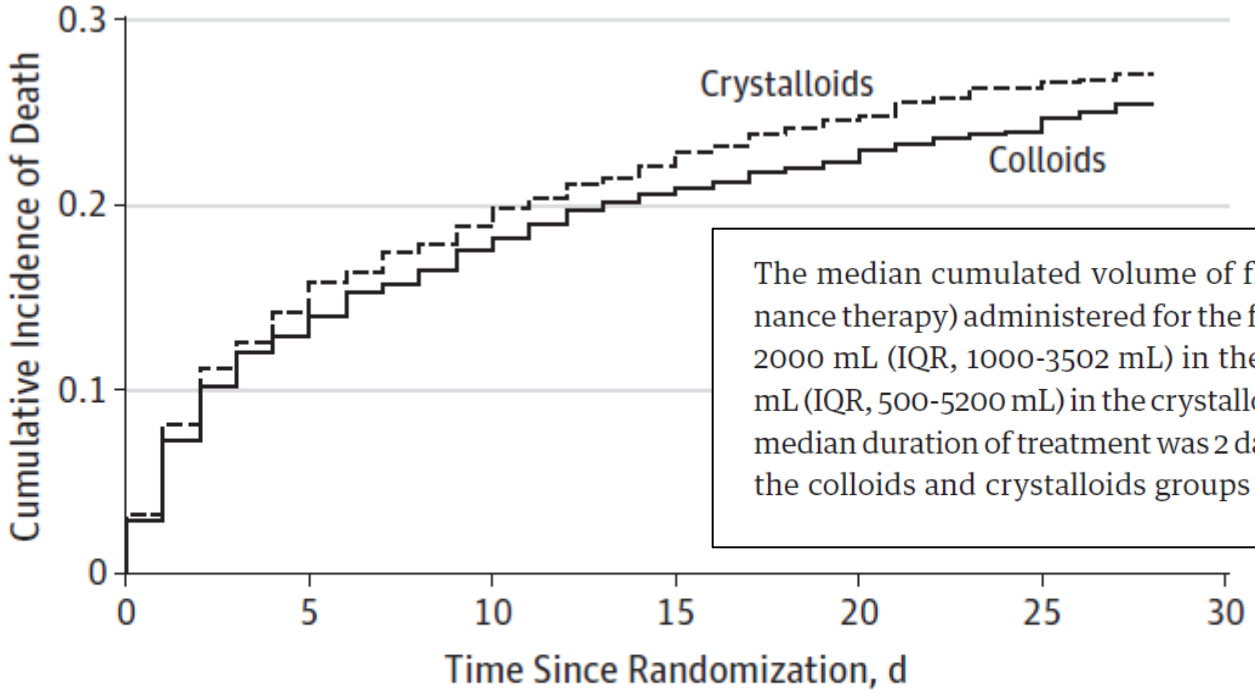


The median cumulated volume of fluid (except for maintenance therapy) administered for the first 7 days in the ICU was 2000 mL (IQR, 1000-3502 mL) in the colloids group vs 3000 mL (IQR, 500-5200 mL) in the crystalloids group ($P < .001$). The median duration of treatment was 2 days (IQR, 1-3 days) in both the colloids and crystalloids groups ($P = .93$).

No. at risk

Colloids	1414	1233	1167	1124	1099	1076
Crystalloids	1443	1239	1172	1124	1089	1064

Effects of Fluid Resuscitation With Colloids vs Crystalloids on Mortality in Critically Ill Patients Presenting With Hypovolemic Shock

The CRISTAL Randomized Trial

JAMA. doi:10.1001/jama.2013.280502
Published online October 9, 2013.

	Colloids Group, No.		Crystalloids Group, No.		
	Patients	Deaths	Patients	Deaths	HR (95% CI)
28-d Mortality					
Entire population	1414	359	1443	390	0.92 (0.80-1.07)
HES vs isotonic saline	645	149	1035	275	0.83 (0.68-1.01)
Gelatins vs isotonic saline	281	69	1035	275	0.90 (0.69-1.17)
HES vs Ringer solution	645	149	72	22	0.71 (0.45-1.11)
Gelatins vs Ringer solution	281	69	72	22	0.78 (0.48-1.26)
Albumin vs isotonic saline	80	24	1035	275	1.10 (0.72-1.68)
90-d Mortality					
Entire population	1414	434	1443	493	0.88 (0.77-0.99)
HES vs isotonic saline	645	181	1035	346	0.79 (0.66-0.95)
Gelatins vs isotonic saline	281	84	1035	346	0.87 (0.68-1.10)
HES vs Ringer solution	645	181	72	26	0.72 (0.48-1.09)
Gelatins vs Ringer solution	281	84	72	26	0.80 (0.51-1.24)
Albumin vs isotonic saline	80	28	1035	346	1.02 (0.69-1.50)

Anwendungsbeschränkung für HES (Hydroxyethlystärke-haltige Arzneimittel)

Datum
12.11.2013

Zusammenfassung der neuen Empfehlungen

- **HES-haltige Infusionslösungen sollen nur für die Behandlung einer Hypovolämie aufgrund akuten Blutverlustes verwendet werden, wenn die Gabe von kristalloiden Infusionslösungen alleine nicht als ausreichend betrachtet wird.**

- **HES-haltige Infusionslösungen sollten in der niedrigsten wirksamen Dosis und so kurz wie möglich angewendet werden. Die Behandlung sollte sich an den Ergebnissen kontinuierlicher hämodynamischer Überwachung orientieren, so dass die Infusion beendet werden kann, sobald die hämodynamischen Ziele erreicht wurden.**

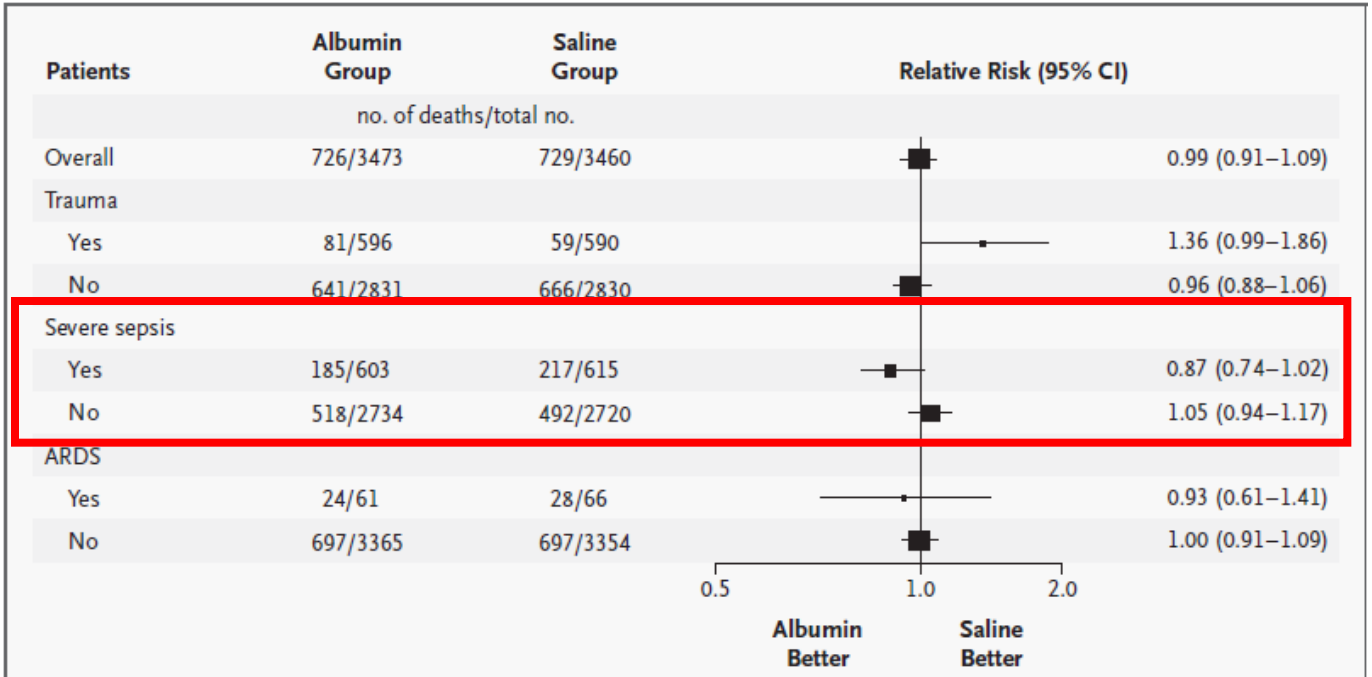
- **HES-haltige Infusionslösungen sind nun kontraindiziert bei:**
  - **Sepsis**
  - **Verbrennungen**
  - **Eingeschränkter Nierenfunktion oder bei Nierenersatztherapie**
  - **Intrakranieller oder zerebraler Blutung**
  - **Kritisch kranken Patienten (in der Regel auf der Intensivstation)**
  - **Hyperhydratation, einschließlich Patienten mit Lungenödem**
  - **Dehydratation**
  - **Schwerer Gerinnungsstörung**
  - **Schweren Leberfunktionsstörungen**

- **Es liegen keine ausreichend robusten Langzeitdaten zur Sicherheit von HES bei chirurgischen und Trauma-Patienten vor. Der erwartete Nutzen der Behandlung sollte sorgfältig gegen die**

A Comparison of Albumin and Saline for Fluid Resuscitation in Intensive Care Unit

METHODS

We randomly assigned patients who had been admitted to the ICU to receive either 4 percent albumin or normal saline for intravascular-fluid resuscitation during the next 28 days. The primary outcome measure was death from any cause during the 28-day period after randomization.



Patients	Albumin Group	Saline Group	Relative Risk (95% CI)
	no. of deaths/total no.		
Overall	726/3473	729/3460	0.99 (0.91–1.09)
Trauma			
Yes	81/596	59/590	1.36 (0.99–1.86)
No	641/2831	666/2830	0.96 (0.88–1.06)
Severe sepsis			
Yes	185/603	217/615	0.87 (0.74–1.02)
No	518/2734	492/2720	1.05 (0.94–1.17)
ARDS			
Yes	24/61	28/66	0.93 (0.61–1.41)
No	697/3365	697/3354	1.00 (0.91–1.09)

Figure 2. Relative Risk of Death from Any Cause among All the Patients and among the Patients in the Six Predefined Subgroups.

S. Finfer et al.

N Engl J Med 350:2247-2256 (2004)

ORIGINAL ARTICLE

Albumin Replacement in Patients with Severe Sepsis or Septic Shock

Pietro Caironi, M.D., Gianni Tognoni, M.D., Serge Masson, Ph.D., Roberto Fumagalli, M.D., Antonio Pesenti, M.D., Marilena Romero, Ph.D., Caterina Fanizza, M.Stat., Luisa Caspani, M.D., Stefano Faenza, M.D., Giacomo Grasselli, M.D., Gaetano Iapichino, M.D., Massimo Antonelli, M.D., Vieri Parrini, M.D., Gilberto Fiore, M.D., Roberto Latini, M.D., and Luciano Gattinoni, M.D., for the ALBIOS Study Investigators*

METHODS

In this multicenter, open-label trial, we randomly assigned 1818 patients with severe sepsis, in 100 intensive care units (ICUs), to receive either 20% albumin and crystalloid solution or crystalloid solution alone. In the albumin group, the target serum albumin concentration was 30 g per liter or more until discharge from the ICU or 28 days after randomization. The primary outcome was death from any cause at 28 days. Secondary outcomes were death from any cause at 90 days, the number

This article was published on March 18, 2014, at NEJM.org.

Letter to the Editor

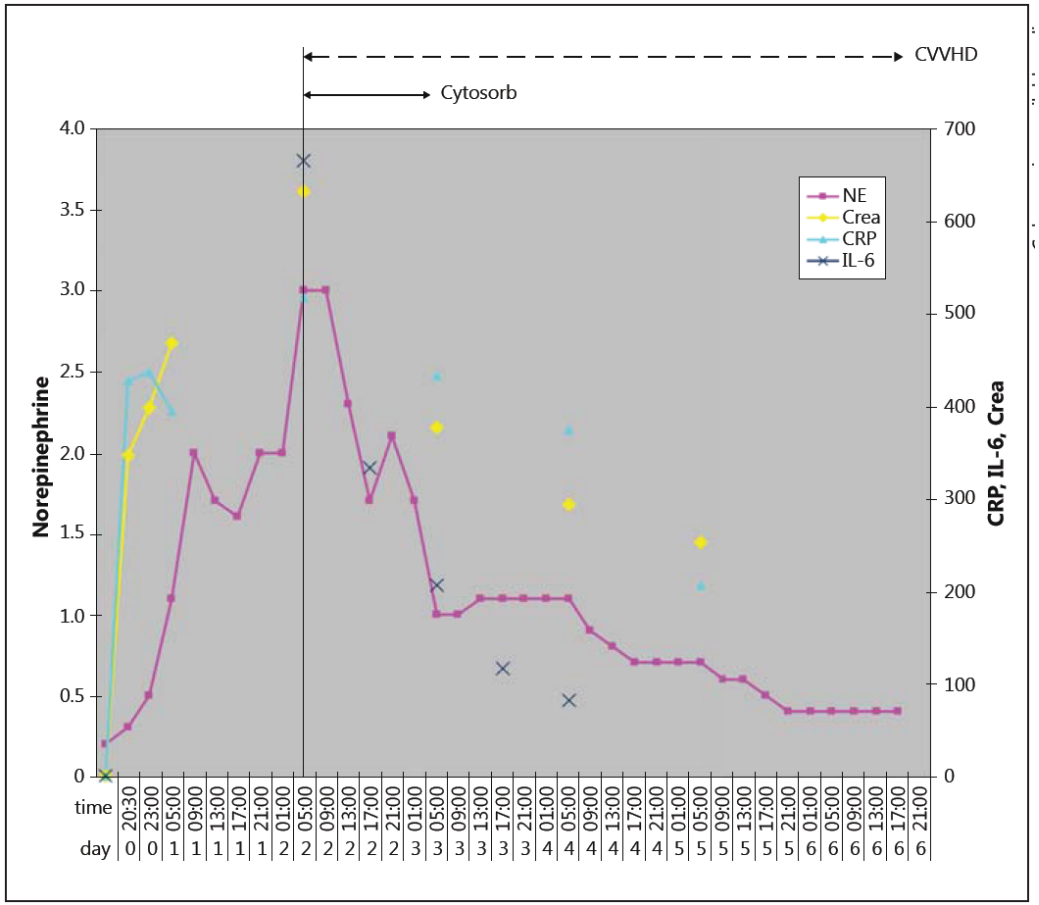
Blood Purification

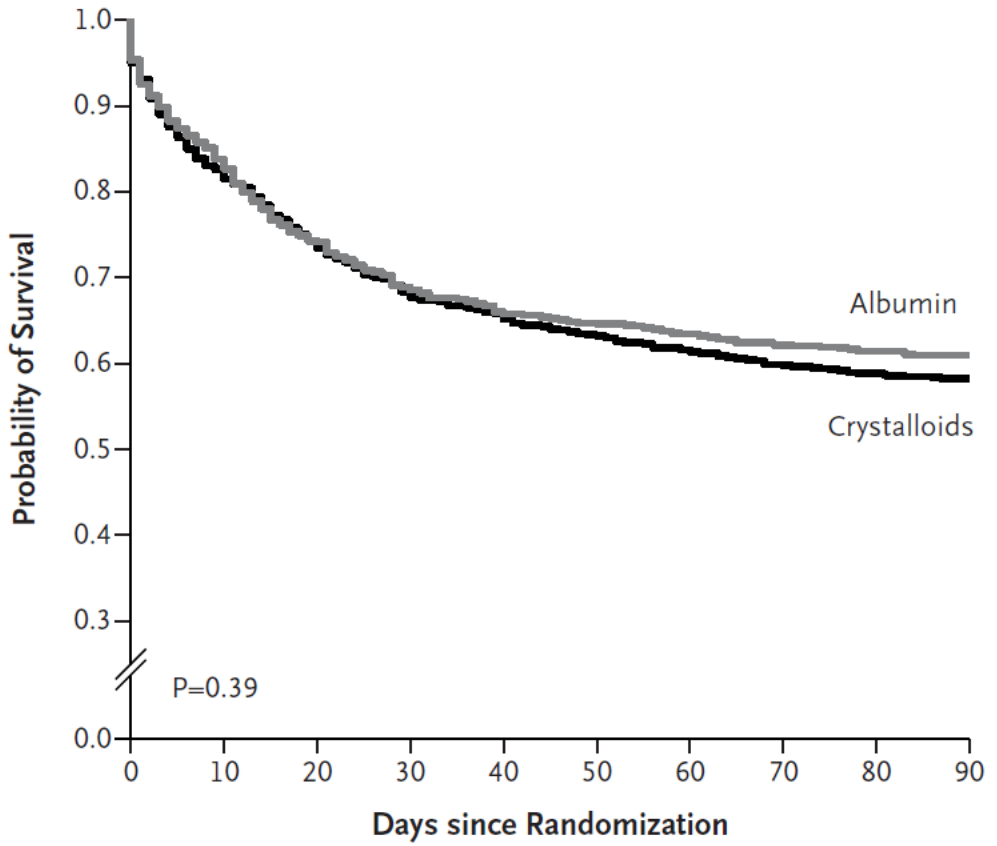
Blood Purif 2013;35:314–315
DOI: 10.1159/000351206

Published online: July 31, 2013

Improvement of Hemodynamic and Inflammatory Parameters by Combined Hemoadsorption and Hemodiafiltration in Septic Shock: A Case Report

Steffen R. Mitzner[a] Martin Gloger[b] Jörg Henschel[b] Sebastian Koball[a]





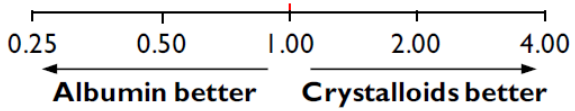
No. at Risk

Albumin	903	733	647	597	567	556	545	535	529	523
Crystalloids	907	729	652	598	676	551	538	521	511	504

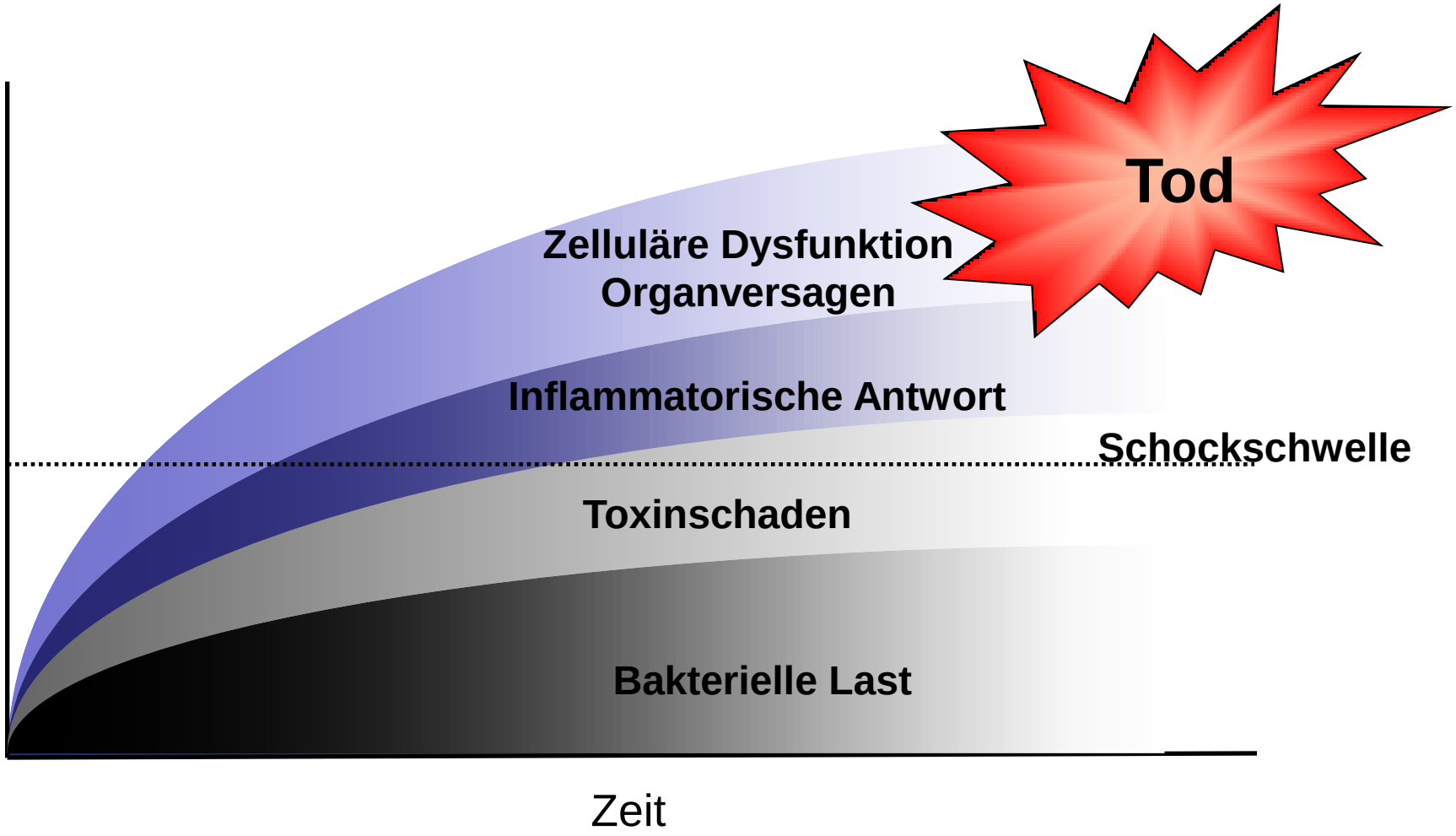
Figure 2. Probability of Survival from Randomization through Day 90.

Figure S3. Risk of Death at 90 Days, according to Subgroup Analysis

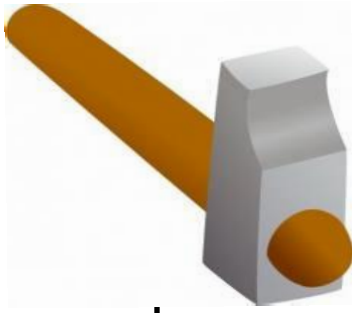
Subgroup	No. of Patients	Albumin	Crystalloids	Relative Risk (95% CI)	P value
		no. of deaths (%)			
All patients	1781	365 (41.1)	389 (43.6)	0.94 (0.85-1.05)	0.29
Time of enrollment					0.46
< 6 hours	569	115 (40.6)	116 (40.6)	1.00 (0.82-1.22)	0.99
6-24 hours	1212	250 (41.3)	273 (45.0)	0.92 (0.81-1.05)	0.20
Septic shock at enrollment					0.03
No	660	122 (37.0)	108 (32.7)	1.13 (0.92-1.39)	0.25
Yes	1121	243 (43.6)	281 (49.9)	0.87 (0.77-0.99)	0.03



Schadensparadigma des septischen Schocks: die goldene Stunde

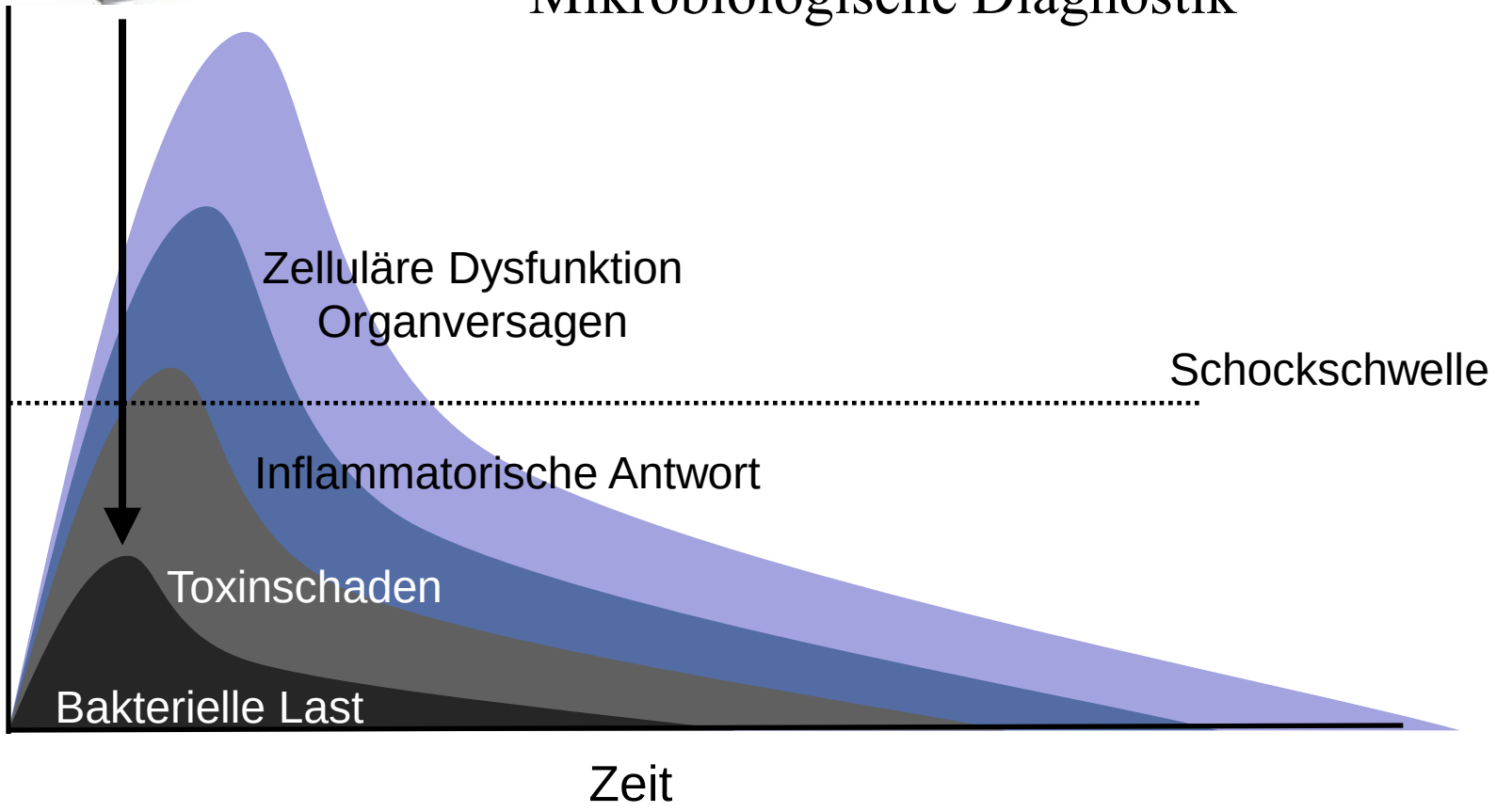


Schadensparadigma des septischen Schocks: die goldene Stunde



Antimikrobielle Therapie / Fokussanierung

→ Mikrobiologische Diagnostik



The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 MAY 1, 2014 VOL. 370 NO. 18

A Randomized Trial of Protocol-Based Care for Early Septic Shock

The ProCESS Investigators*

BACKGROUND

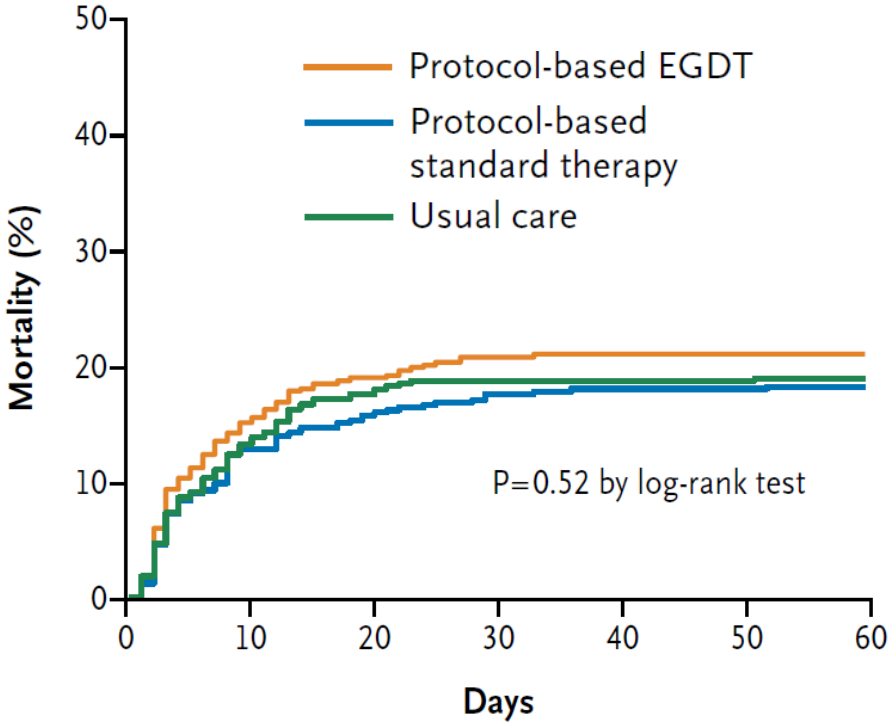
In a single-center study published more than a decade ago involving patients presenting to the emergency department with severe sepsis and septic shock, mortality was markedly lower among those who were treated according to a 6-hour protocol of early goal-directed therapy (EGDT), in which intravenous fluids, vasopressors, inotropes, and blood transfusions were adjusted to reach central hemodynamic targets, than among those receiving usual care. We conducted a trial to determine whether these findings were generalizable and whether all aspects of the protocol were necessary.

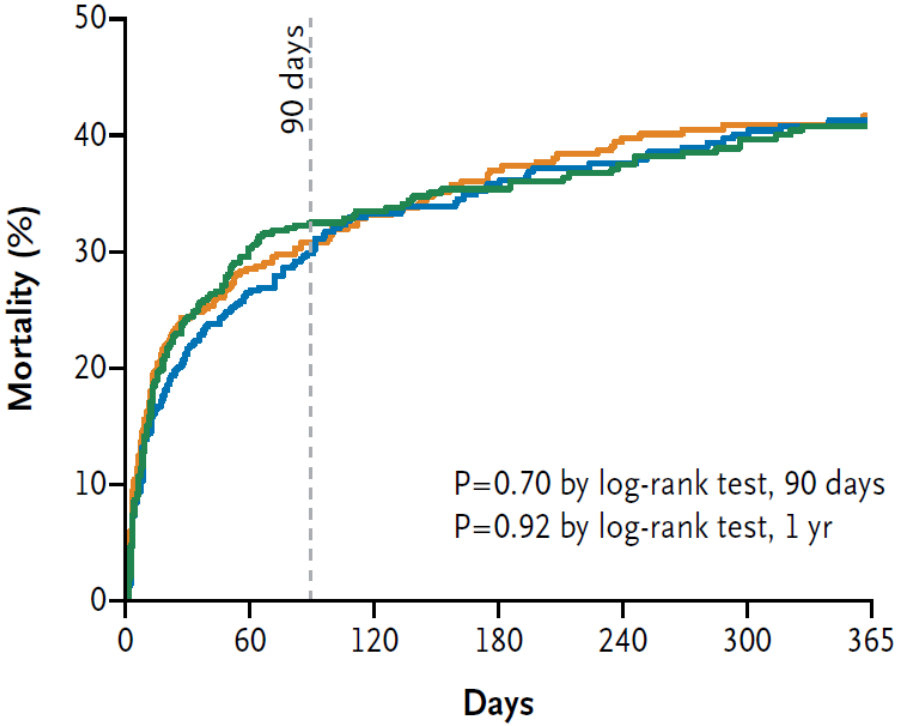
Table 2. Outcomes.*

Outcome	Protocol-based EGDT (N=439)	Protocol-based Standard Therapy (N=446)	Usual Care (N=456)	P Value†
Death — no./total no. (%)				
In-hospital death by 60 days: primary outcome	92/439 (21.0)	81/446 (18.2)	86/456 (18.9)	0.83‡
Death by 90 days	129/405 (31.9)	128/415 (30.8)	139/412 (33.7)	0.66
New organ failure in the first week — no./total no. (%)				
Cardiovascular	269/439 (61.3)	284/446 (63.7)	256/456 (56.1)	0.06
Respiratory	165/434 (38.0)	161/441 (36.5)	146/451 (32.4)	0.19
Renal	12/382 (3.1)	24/399 (6.0)	11/397 (2.8)	0.04
Duration of organ support — days§				
Cardiovascular	2.6±1.6	2.4±1.5	2.5±1.6	0.52
Respiratory	6.4±8.4	7.7±10.4	6.9±8.2	0.41
Renal	7.1±10.8	8.5±12	8.8±13.7	0.92
Use of hospital resources				
Admission to intensive care unit — no. (%)	401 (91.3)	381 (85.4)	393 (86.2)	0.01
Stay in intensive care unit among admitted patients — days	5.1±6.3	5.1±7.1	4.7±5.8	0.63
Stay in hospital — days	11.1±10	12.3±12.1	11.3±10.9	0.25
Discharge status at 60 days — no. (%)				
Not discharged	3 (0.7)	8 (1.8)	2 (0.4)	0.82
Discharged to a long-term acute care facility	16 (3.6)	22 (4.9)	22 (4.8)	
Discharge to another acute care hospital	8 (1.8)	2 (0.4)	5 (1.1)	
Discharged to nursing home	71 (16.2)	93 (20.9)	88 (19.3)	
Discharged home	236 (53.8)	227 (50.9)	235 (51.5)	
Other or unknown	13 (3.0)	13 (2.9)	18 (3.9)	
Serious adverse events — no. (%)¶	23 (5.2)	22 (4.9)	37 (8.1)	0.32

Randomized Trial of Protocol-Based Care for Early Septic Shock

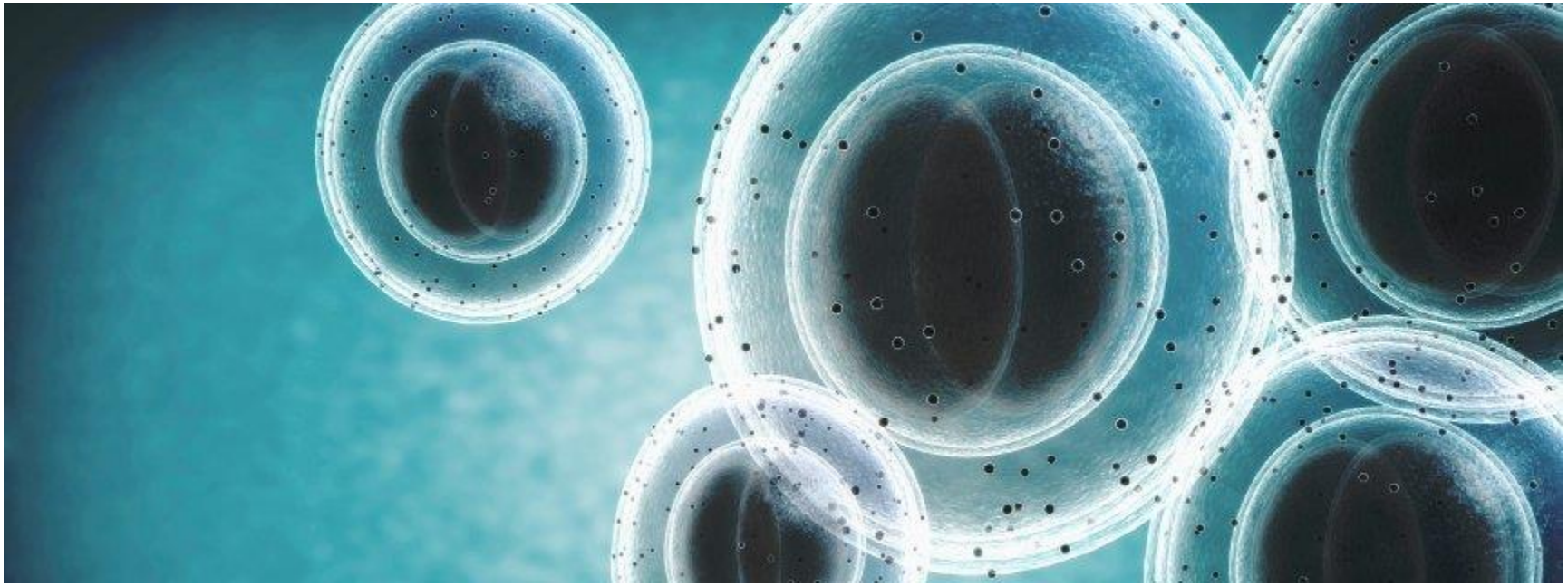
The ProCESS Investigators*





SPIEGEL ONLINE

Freitag, 28.03.2014 – 15:35 Uhr



Krankenhausinfektionen: Experten streiten über Zahl der Todesfälle

Multiresistente Bakterien (grafische Illustration): Klinikinfektionen sind in Deutschland ein großes Problem

Tausende Menschen sterben jährlich an den Folgen einer Klinik-Infektion. Experten für Krankenhaushygiene gehen davon aus, dass die Zahl viel höher ist als bisher vermutet. Gesichert sind die Schätzungen aber nicht. Fest steht nur: Viele Fälle wären vermeidbar.

Wie groß das Ausmaß nosokomialer Infektionen jedoch wirklich ist, darüber streiten sich Experten unterschiedlicher Interessengruppen. Auch bei der Pressekonferenz, zu der die Deutsche Gesellschaft für Krankenhaushygiene (DGKH) am Freitag in Berlin geladen hatte, ist das erneut deutlich geworden: Laut einer Untersuchung der DGKH muss man bundesweit von 900.000 nosokomialen Infektionen jährlich ausgehen. Demnach sterben pro Jahr rund 30.000 Menschen an einer solchen Klinikinfektion - weit mehr, als bisher angenommen. Diesen Zahlen aber widerspricht die Deutsche Krankenhausgesellschaft (DKG). Bisherige Schätzungen gingen von 10.000 bis 15.000 Todesfällen jährlich aus. Die DKG dagegen führt offizielle Zahlen seitens des Nationalen Referenzzentrums ins Feld und spricht von 2000 bis 4500 Patienten, die jährlich an einer vermeidbaren Klinikinfektion sterben.

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JUNE 13, 2013 VOL. 368 NO. 24

Targeted versus Universal Decolonization to Prevent ICU Infection

Susan S. Huang, M.D., M.P.H., Edward Septimus, M.D., Ken Kleinman, Sc.D., Julia Moody, M.S., Jason Hickok, M.B.A., R.N., Taliser R. Avery, M.S., Julie Lankiewicz, M.P.H., Adrijana Gombosev, B.S., Leah Terpstra, B.A., Fallon Hartford, M.S., Mary K. Hayden, M.D., John A. Jernigan, M.D., Robert A. Weinstein, M.D., Victoria J. Fraser, M.D., Katherine Haffenreffer, B.S., Eric Cui, B.S., Rebecca E. Kaganov, B.A., Karen Lolans, B.S., Jonathan B. Perlin, M.D., Ph.D., and Richard Platt, M.D., for the CDC Prevention Epicenters Program and the AHRQ DECIDE Network and Healthcare-Associated Infections Program*

N Engl J Med 2013;368:2255-65.
DOI: 10.1056/NEJMoa1207290

CONCLUSIONS

In routine ICU practice, universal decolonization was more effective than targeted decolonization or screening and isolation in reducing rates of MRSA clinical isolates and bloodstream infection from any pathogen. (Funded by the Agency for Healthcare Research and the Centers for Disease Control and Prevention; REDUCE MRSA ClinicalTrials.gov number, NCT00980980.)

Zentrale Aussagen:

- Cuffdruck auf 20 – 30 cm H_2O einstellen
- Subglottische Absaugung bei mehr als 72 Stunden Beatmungsdauer
- Umintubation muss dabei sorgfältig abgewogen werden
- Keine Aussage zu kontinuierlicher versus intermittierender Absaugung
- Keine Empfehlung zum generellen Einsatz einer SDD

Bundesgesundheitsbl 2013 · 56:1578–1590

Prävention der nosokomialen beatmungsassoziierten Pneumonie

Empfehlung der Kommission für Krankenhaushygiene und Infektionsprävention (KRINKO) beim Robert Koch-Institut

Krinsley *et al. Critical Care* 2013, **17**:R37
http://ccforum.com/content/17/2/R37

CRITICAL CARE

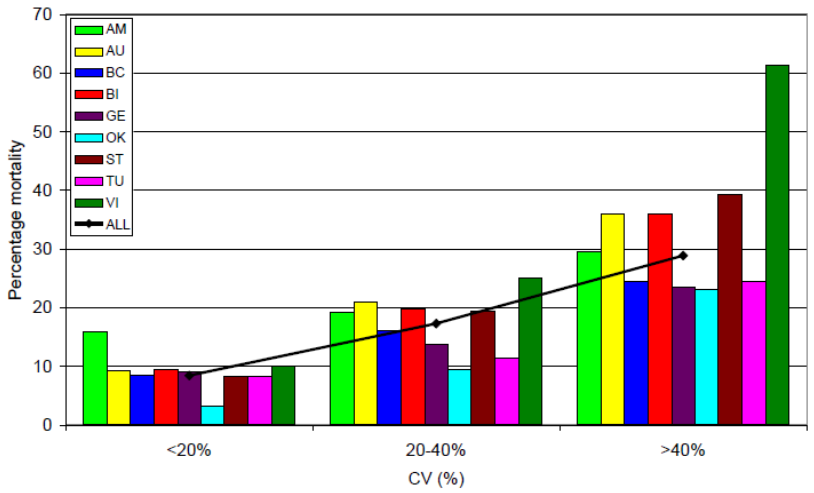
RESEARCH Open Access

Diabetic status and the relation of the three domains of glycemic control to mortality in critically ill patients: an international multicenter cohort study

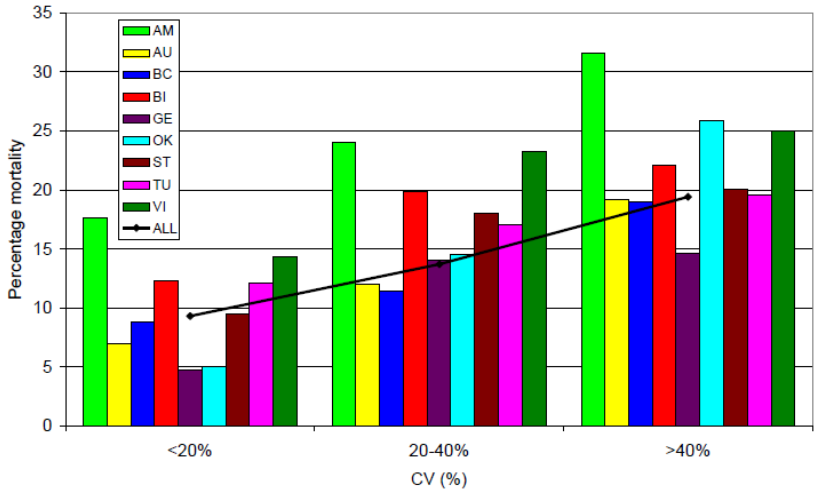
James S Krinsley[1*], Moritoki Egi[2], Alex Kiss[3], Amin N Devendra[4], Philipp Schuetz[5], Paula M Maurer[6], Marcus J Schultz[7], Roosmarijn TM van Hooijdonk[7], Morita Kiyoshi[2], Iain MJ Mackenzie[8], Djillali Annane[9], Peter Stow[10], Stanley A Nasraway[11], Sharon Holewinski[11], Ulrike Holzinger[12], Jean-Charles Preiser[13], Jean-Louis Vincent[13] and Rinaldo Bellomo[14]

Methods: This is a retrospective analysis of prospectively collected data involving 44,964 patients admitted to 23 intensive care units (ICUs) from nine countries, between February 2001 and May 2012. We analyzed mean blood glucose concentration (BG), coefficient of variation (CV), and minimal BG and created multivariable models to analyze their independent association with mortality. Patients were stratified according to the diagnosis of diabetes.

A. Non-diabetics



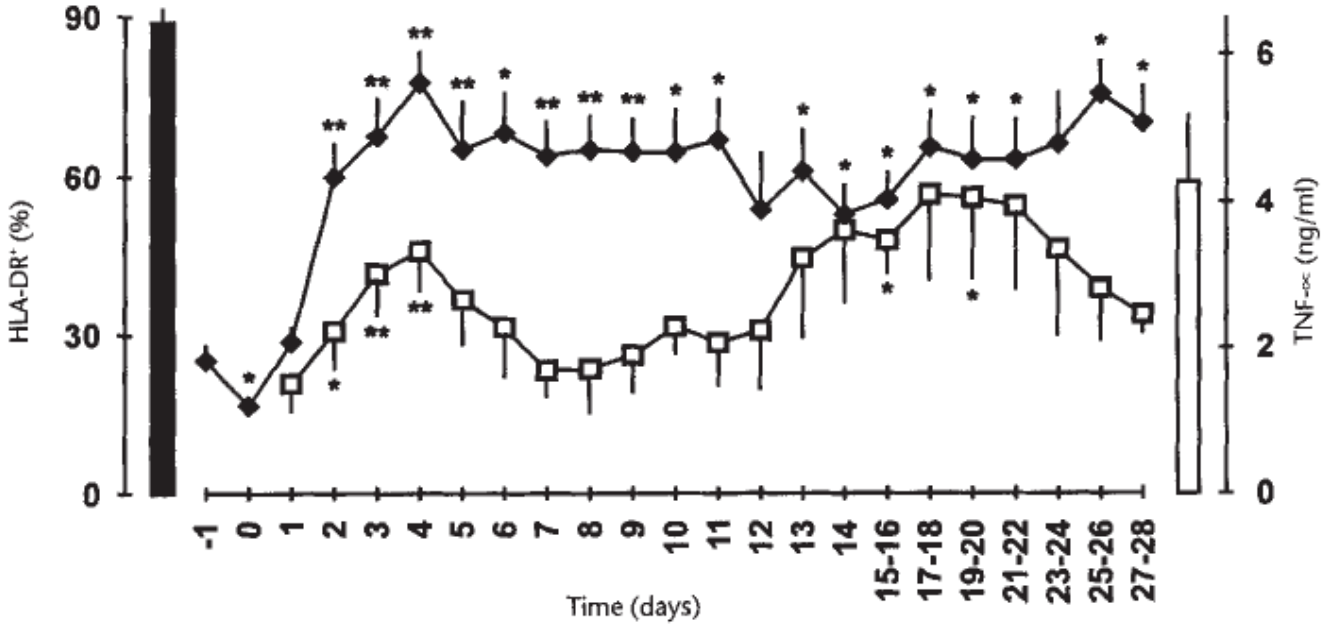
B. Diabetics



Monocyte deactivation in septic patients: Restoration by IFN-γ treatment

NATURE MEDICINE • VOLUME 3 • NUMBER 6 • JUNE 1997

WOLF-DIETRICH DÖCKE[1], FELIX RANDOW[1], UTA SYRBE[1], DIETMAR KRAUSCH[2], KHUSRU ASADULLAH[1], PETRA REINKE[3], HANS-DIETER VOLK[1], WOLFGANG KOX[2]



ιtic patients with IFN-γ restores monocytic HLA-DR expression and *in vitro* LPS-induced TNF-α secretion. F

ORIGINAL ARTICLE

A Randomized Trial of Glutamine and Antioxidants in Critically Ill Patients

Daren Heyland, M.D., John Muscedere, M.D., Paul E. Wischmeyer, M.D., Deborah Cook, M.D., Gwynne Jones, M.D., Martin Albert, M.D., Gunnar Elke, M.D., Mette M. Berger, M.D., Ph.D., and Andrew G. Day, M.Sc., for the Canadian Critical Care Trials Group

N Engl J Med 2013;368:1489-97.

METHODS

In this blinded 2-by-2 factorial trial, we randomly assigned 1223 critically ill adults in 40 intensive care units (ICUs) in Canada, the United States, and Europe who had multiorgan failure and were receiving mechanical ventilation to receive supplements of glutamine, antioxidants, both, or placebo. Supplements were started within 24 hours after admission to the ICU and were provided both intravenously and enterally. The primary outcome was 28-day mortality. Because of the interim-analysis plan, a P value of less than 0.044 at the final analysis was considered to indicate statistical significance.

patients to receive glutamine supplementation (0.35 g per kilogram of body weight per day intravenously according to ideal body weight, provided as 0.50 g of the dipeptide alanyl-glutamine [Dipeptiven, Fresenius Kabi] per kilogram per day given intravenously and 42.5 g of alanyl-glutamine and glycine-glutamine dipeptides, which provide 30 g of glutamine, per day given enterally) or matching placebo solutions. In addition, patients were randomly assigned to receive 500 μg of selenium intravenously (Selenase, Biosyn) plus the following vitamins and minerals enterally: 300 μg of selenium, 20 mg of zinc, 10 mg of beta carotene, 500 mg of vitamin E, and 1500 mg of vitamin C.

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RESULTS

There was a trend toward increased mortality at 28 days among patients who received glutamine as compared with those who did not receive glutamine (32.4% vs. 27.2%; adjusted odds ratio, 1.28; 95% confidence interval [CI], 1.00 to 1.64; P=0.05). In-hospital mortality and mortality at 6 months were significantly higher among those who received glutamine than among those who did not. Glutamine had no effect on rates of organ failure or infectious complications. Antioxidants had no effect on 28-day mortality (30.8%, vs. 28.8% with no antioxidants; adjusted odds ratio, 1.09; 95% CI, 0.86 to 1.40; P=0.48) or any other secondary end point. There were no differences among the groups with respect to serious adverse events (P=0.83).